

PCT/26515

FILE 'REGISTRY' ENTERED AT 10:26:25 ON 17 OCT 2002

- Key terms

=> e polyethylene glycol/cn 5

E1 1 POLYETHYLENE FIBERS, ETHYLENE-PROPENE/CN
E2 1 POLYETHYLENE GLYCOL METHOXYACETIC ACID ESTER FORMATE/CN
N
E3 1 --> POLYETHYLENE GLYCOL/CN
E4 1 POLYETHYLENE GLYCOL (1-AZIRIDINYL)ETHYL ETHER/CN
E5 1 POLYETHYLENE GLYCOL (400) ESTERS OF COCONUT OIL FATTY ACIDS/CN

=> s e3

L1 1 "POLYETHYLENE GLYCOL"/CN

=> e "polyethylene glycol, activated"/cn 5

E1 1 POLYETHYLENE GLYCOL UNDECYL ETHER PHOSPHATE/CN
E2 1 POLYETHYLENE GLYCOL XYLITOL ETHER/CN
E3 0 --> POLYETHYLENE GLYCOL, ACTIVATED/CN
E4 1 POLYETHYLENE GLYCOL-.ALPHA., .ALPHA., .ALPHA.', .ALPHA.'-TETRAMETHYL-M-XYLYLENE DIISOCYANATE-TRIMETHYLOLPROPANE COPOLYMER/CN
E5 1 POLYETHYLENE GLYCOL-.ALPHA., .OMEGA.-DI (SULFOPHENYL-4-I SOTHIOCYANATE) /CN

=> e ".alpha.-carboxymethyl, .omega.-carboxymethoxypolyoxyethylene"/cn 5

E1 1 .ALPHA.-CARBOXYLASE/CN
E2 1 .ALPHA.-CARBOXYLESTERASE/CN
E3 0 --> .ALPHA.-CARBOXYMETHYL, .OMEGA.-CARBOXYMETHOXYPOLYOXYETHYLENE/CN
E4 1 .ALPHA.-CARBOXYPHENYLACETIC ACID/CN
E5 1 .ALPHA.-CARBOXYPHENYLACETYL CHLORIDE/CN

=> e poe/cn 5

E1 1 PODPCARPAN-16-OIC ACID, 12,13-EPOXY-/CN
E2 1 PODURAN/CN
E3 0 --> POE/CN
E4 1 POE 220/CN
E5 1 POE 68/CN

=> e "polyoxyethylene (.alpha.-carboxymethyl, .omega.-carboxymethoxypolyoxyethylene)"/cn 5

E1 1 POLYOXYETHYLENATED POLY(OXYPROPYLENE)/CN
E2 1 POLYOXYETHYLENATED (14) 3,4-DIOCTYLPHENOL/CN
E3 0 --> POLYOXYETHYLENE (.ALPHA.-CARBOXYMETHYL, .OMEGA.-CARBOXYMETHOXYPOLYOXYETHYLENE)/CN
E4 1 POLYOXYETHYLENE (10) LANOLIN ETHER, ACETYLATED/CN
E5 1 POLYOXYETHYLENE (13) OCTYLPHENYL ETHER/CN

=> d que 15; d kwic 1-3

L3 52030 SEA FILE=REGISTRY ABB=ON PLU=ON ?CARBOXYMETHYL?/CNS
L4 698 SEA FILE=REGISTRY ABB=ON PLU=ON ?POLYOXYETHYLENE?/CNS
L5 3 SEA FILE=REGISTRY ABB=ON PLU=ON L3(S)L4

L5 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2002 ACS

OTHER NAMES:

CN N-.beta.-Hydroxylauryl-N,N-bis (polyoxyethylene) -N-carboxymethylammonium betaine sodium salt

L5 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2002 ACS

PCT/26515

OTHER NAMES:

CN **Lauroyloxypolyoxyethylene carboxymethyl ether sodium salt**

L5 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2002 ACS

OTHER NAMES:

CN **Polyoxyethylene lauryl carboxymethyl ether sodium salt**

E ".ALPHA.-CARBOXYMETHYL-.OMEGA.-CARBOXYMETHOXYL POLYOXYE
E ".ALPHA.-CARBOXYMETHYL-.OMEGA.-CARBOXYMETHOXYLPOLYOXYET
E ".ALPHA.-CARBOXYMETHYL-.OMEGA.-CARBOXYMETHOXPOLYOXYETH
E ".ALPHA.-CARBOXYMETHYL-.OMEGA.-CARBOXYMETHOXY POLYOXYET

FILE 'HCAPLUS' ENTERED AT 10:50:27 ON 17 OCT 2002

L1 1 SEA FILE=REGISTRY ABB=ON PLU=ON "POLYETHYLENE GLYCOL"/C
N
L6 65224 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 OR APEG OR ACTIVAT?(W
) (PEG OR (POLYETHYLENE OR POLY ETHYLENE) (W) GLYCOL)
L10 42680 SEA FILE=HCAPLUS ABB=ON PLU=ON POLYOXYETHYLENE OR
CARBOXYMETHOXPOLYOXYETHYLENE OR METHOXPOLYOXYETHYLENE
OR POLY(W) (OXY ETHYLENE OR OXYETHYLENE) OR POLYOXY
ETHYLENE
L11 8 SEA FILE=HCAPLUS ABB=ON PLU=ON L10(10A) (ALPHA(W) (CARBOX
YMETHYL OR CARBOXY(W) (ME OR METHYL)))
L16 5 SEA FILE=HCAPLUS ABB=ON PLU=ON POE(S) (CARBOXY(W) (METHYL
? OR ME) OR CARBOXYMETHYL?)
L17 448 SEA FILE=HCAPLUS ABB=ON PLU=ON (L6 OR L11 OR L16) AND
(HB OR HEMOGLOBIN OR HAEMOGLOBIN)
L18 1 SEA FILE=REGISTRY ABB=ON PLU=ON "NYLON 66"/CN
L19 1 SEA FILE=REGISTRY ABB=ON PLU=ON POSIDYNE/CN
L20 37 SEA FILE=HCAPLUS ABB=ON PLU=ON L17 AND (L18 OR L19 OR
NYLON 66 OR POSIDYNE OR FILTER? OR FILTR?)

L20 ANSWER 1 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:428940 HCAPLUS

DOCUMENT NUMBER: 137:2748

TITLE: Methods for the synthesis of a modified
hemoglobin solution

INVENTOR(S): Privalle, Christopher Thomas; Stacey, Cyrus
John; Talarico, Todd Lewis

PATENT ASSIGNEE(S): Apex Bioscience, Inc., USA

SOURCE: PCT Int. Appl., 45 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2002044214 | A1 | 20020606 | WO 2001-US43877 | 20011114 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD | | | | |

Searcher : Shears 308-4994

PCT/26515

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,
TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
TD, TG

US 2002099175 A1 20020725 US 2001-930905 20010816

AU 2002017823 A5 20020611 AU 2002-17823 20011114

PRIORITY APPLN. INFO.:

US 2000-253758P P 20001129

US 2001-930905 A 20010816

WO 2001-US43877 W 20011114

AB The invention concerns a **filtration** step during the
Hb purifn. process that substantially decreases viral
communication of a **Hb** soln. The **filtration**
means can be used to sep. **Hb** and several endogenous
antioxidant enzymes from red blood cell stroma and potential
adventitious agents. The purified **Hb**/antioxidant compn.
is then subjected to a chem. modification process. The resulting
modified **Hb**/antioxidant compn. is then fractionated to
remove unmodified **Hb** species and residual reactants,
formulated in electrolytes and rendered sterile. The resulting
modified **Hb** product is substantially free of viral
contamination and contains at least one endogenous antioxidant
enzyme that retains antioxidant activity.

IT 25322-68-3DP, conjugates with pyridoxalated **Hb**
RL: BUU (Biological use, unclassified); SPN (Synthetic preparation);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(PHP; methods for synthesis of a modified **Hb** soln.)

IT 25322-68-3
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL
(Biological study); USES (Uses)
(methods for synthesis of a modified **Hb** soln.)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR
THIS RECORD. ALL CITATIONS AVAILABLE IN
THE RE FORMAT

L20 ANSWER 2 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:360213 HCAPLUS

DOCUMENT NUMBER: 134:337926

TITLE: Method using fumed metallic oxides for isolating
DNA from a proteinaceous medium and kit for
performing method

INVENTOR(S): Krupey, John

PATENT ASSIGNEE(S): Ligochem, Inc., USA

SOURCE: PCT Int. Appl., 66 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|---|----------|-----------------|----------|
| WO 2001034844 | A1 | 20010517 | WO 2000-US31005 | 20001113 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, | | | |

Searcher : Shears 308-4994

PCT/26515

TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE,
TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD,
TG
EP 1244811 A1 20021002 EP 2000-977161 20001113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,
PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.: US 1999-164608P P 19991110
WO 2000-US31005 W 20001113
AB A method is described for isolating DNA from a proteinaceous medium
such as whole blood, **Hb**-contg. urine or saliva. Also
disclosed are test kits for practicing the method. Guanidine
thiocyanate in sodium acetate pH 7.0 soln. contg. EDTA was added to
Hb-contg. and white blood cell-contg. urine samples to
disrupt the cells, dissoc. the DNA histone complex, and release free
DNA into soln. Contaminating proteins were removed by treating the
chaotrope-contg. urine with a water-insol. cross-linked polymeric
acid, trade name ProCipitate. The DNA was captured with titanium
oxide P25, the aggregate was washed, and DNA was recovered by
treatment with NaOH.
IT **25322-68-3D**, Polyethylene glycol, with bound fumed metal
oxides
RL: BUU (Biological use, unclassified); BIOL (Biological study);
USES (Uses)
(DNA isolation from proteinaceous medium using fumed metallic
oxides and kit for performing method)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR
THIS RECORD. ALL CITATIONS AVAILABLE IN
THE RE FORMAT

L20 ANSWER 3 OF 37 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:260097 HCAPLUS
DOCUMENT NUMBER: 132:284201
TITLE: Method for production of stroma-free
hemoglobin
INVENTOR(S): Winslow, Robert M.; Vandegriff, Kim D.
PATENT ASSIGNEE(S): Sangart, Inc., USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|-----------------|----------|
| WO 2000021591 | A1 | 20000420 | WO 1999-US24149 | 19991015 |
| W: | AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| EP 1121165 | A1 | 20010808 | EP 1999-954950 | 19991015 |

Searcher : Shears 308-4994

PCT/26515

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,
PT, IE, FI

| | | | | |
|------------------------|----|----------|-----------------|------------|
| BR 9915734 | A | 20011002 | BR 1999-15734 | 19991015 |
| JP 2002527149 | T2 | 20020827 | JP 2000-575563 | 19991015 |
| PRIORITY APPLN. INFO.: | | | US 1998-104319P | P 19981015 |
| | | | US 1999-122180P | P 19990301 |
| | | | WO 1999-US24149 | W 19991015 |

AB The method employs a com.-available blood cell separator comprising a computer-controlled centrifuge having a rotor into which a blood processing bag contg. donor blood is placed. Once the blood is collected, the process is performed entirely within the enclosed centrifuge bowl, preferably in situ at the donor collection site. In the first step, the blood is centrifuged to sep. the plasma from the cellular components. After isolation of the red blood cells from other blood components, the red cells are washed with normal saline or other soln. The red blood cells are then lysed by hypotonic shock to sep. the red cell membranes (stroma) and the lysate is collected in a sterile container, leaving only the stroma in the centrifuge bowl. The final product can be used as raw material for any of the **Hb**-based oxygen carriers currently being developed as red cell substitutes. All of the steps are performed within a processing container or blood bag in the bowl centrifuge to minimize handling and maintain sterility. A method for prepg. a modified **Hb** soln. incorporates the steps for producing stroma-free **Hb**, then adding pre-measured reagents to react with the soln. and **filtering** the soln.

IT 25322-68-3, PEG

RL: NUU (Other use, unclassified); PEP (Physical, engineering or chemical process); PROC (Process); USES (Uses)
(method for prodn. of stroma-free **Hb**)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR
THIS RECORD. ALL CITATIONS AVAILABLE IN
THE RE FORMAT

L20 ANSWER 4 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:787313 HCAPLUS

DOCUMENT NUMBER: 132:141908

TITLE: Synthesis and Physicochemical Characterization
of a Series of **Hemoglobin**-Based Oxygen
Carriers: Objective Comparison between Cellular
and Acellular Types

AUTHOR(S): Sakai, Hiromi; Yuasa, Minako; Onuma, Hiroto;
Takeoka, Shinji; Tsuchida, Eishun

CORPORATE SOURCE: Department of Polymer Chemistry, Advanced
Research Institute for Science and Engineering
Waseda University, Tokyo, 169-8555, Japan

SOURCE: Bioconjugate Chemistry (2000), 11(1), 56-64
CODEN: BCCHES; ISSN: 1043-1802

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A series of **Hb** (**Hb**)-based O₂ carriers, acellular and cellular types, were synthesized and their physicochem. characteristics were compared. The acellular type includes intramolecularly cross-linked **Hb** (XLHb), polyoxyethylene (POE)-conjugated pyridoxalated **Hb** (POE-PLP-**Hb**), hydroxyethylstarch-conjugated **Hb** (HES-XLHb), and glutaraldehyde-polymd. XLHb (Poly-XLHb). The cellular type is

Hb-vesicles (HbV) of which the surface is modified with POE (POE-HbV). Their particle diams. are 7 \pm 2, 22 \pm 2, 47 \pm 17, 68 \pm 24, and 224 \pm 76 nm, resp., thus all the materials penetrate across membrane **filters** with 0.4 μ m pore size, though only the POE-HbV cannot penetrate across the **filter** with 0.2 μ m pore size. These characteristics of permeability are important to consider an optimal particle size in microcirculation in vivo. POE-PLP-**Hb** ([**Hb**] = 5 g/dL) showed viscosity of 6.1 cP at 332 s⁻¹ and colloid osmotic pressure (COP) of 70.2 Torr, which are beyond the physiol. conditions (human blood, viscosity = 3-4 cP, COP = ca. 25 Torr). XLHb and Poly-XLHb showed viscosities of 1.0 and 1.5 cp, resp., which are significantly lower than that of blood. COP of POE-HbV is regulated to 20 Torr in 5% human serum albumin (HSA). HES-XLHb and POE-HbV/HSA showed comparable viscosity with human blood. Microscopic observation of human red blood cells (RBC) after mixing blood with POE-PLP-**Hb** or HES-XLHb disclosed aggregates of RBC, a kind of sludge, indicating a strong interaction with RBC, which is anticipated to modify peripheral blood flow in vivo. On the other hand, XLHb and POE-HbV showed no rouleaux or aggregates of RBC. The acellular **Hbs** (P50 = 14-32 Torr) have their specific O₂ affinities detd. by their structures, while that of the cellular POE-HbV is regulated by coencapsulating an appropriate amt. of an allosteric effector (e.g., P50 = 18, 32 Torr). These differences in physicochem. characteristics between the acellular and cellular types indicate the advantages of the cellular type from the physiol. points of view.

IT 25322-68-3D, **Hb** conjugates

RL: BPR (Biological process); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(prepn. and physicochem. properties of **Hb**-based oxygen carriers)

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 5 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:96091 HCAPLUS

DOCUMENT NUMBER: 130:165137

TITLE: Device and method for obtaining clinically significant analyte ratios

INVENTOR(S): Kuo, Hai-Hang; Miller, Carol A.; Wijesuriya, Dayaweere; Yip, Meitak Teresa; Zimmerle, Chris T.

PATENT ASSIGNEE(S): Bayer Corporation, USA

SOURCE: Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|----------|-----------------|----------|
| EP 895084 | A2 | 19990203 | EP 1998-112964 | 19980713 |
| EP 895084 | A3 | 20000315 | | |

PCT/26515

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,
PT, IE, SI, LT, LV, FI, RO

| | | | | |
|-------------|----|----------|----------------|----------|
| US 6436721 | B1 | 20020820 | US 1997-900586 | 19970725 |
| AU 9877440 | A1 | 19990204 | AU 1998-77440 | 19980722 |
| AU 729380 | B2 | 20010201 | | |
| JP 11083856 | A2 | 19990326 | JP 1998-206193 | 19980722 |

PRIORITY APPLN. INFO.: US 1997-900586 A 19970725

AB Disclosed is a method for detg. the concn. of an analyte in a sample of body fluid. The method involves contacting the body fluid sample with a test strip contg. mobile, labeled, specific binding partner for the analyte. The test fluid, analyte, and any complex formed by interaction of the analyte and labeled specific binding partner flow through the strip by capillarity. The strip contains at least one zone for capture of the labeled specific binding partner and at least one sep. zone for retention of the analyte/labeled specific binding partner complex. By detg. the magnitude of the signal from the detectable label in the capture zone(s) and retention zone(s) and detg. a final response signal by correlating signals using an algorithm and no. of zones chosen in a manner that provides a final response signal best suited for the particular assay, the concn. of the analyte can be detd. with greater precision. A test strip for the detn. of creatinine and deoxypyridinoline contained six distinct areas assembled onto a polystyrene backing of 101.6 X 5.0 mm. Area 1 was a creatinine pad made from Whatman 3 mm **filter** paper contg. reagents for the colorimetric detn. of creatinine. Area 2 was a buffer pad for buffering the urine samples. Area 3 contained gold sol-labeled anti-deoxypyridinoline antibody. Area 4 contained 3 capture bands of immobilized deoxypyridinoline. Area 5 had an anti-IgG collection band. Area 6 was an absorbant pad. Areas 1 and 2 were dipped into test urine for 3 s and the strip was placed on the read table of a CLINITEK 50 reflectance spectrometer for anal.

IT 25322-68-3D, Polyethylene glycol, carboxyl-terminated
RL: ARU (Analytical role, unclassified); DEV (Device component use);
ANST (Analytical study); USES (Uses)
(deoxypyridinoline immobilized to, in test strip for creatinine and deoxypyridinoline detn.; device and method for obtaining clin. significant analyte ratios)

L20 ANSWER 6 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:776340 HCAPLUS

DOCUMENT NUMBER: 130:150523

TITLE: Application of hydrophilic polymers in
multichannel flow electrophoresis

AUTHOR(S): Liu, Zheng; Zhao, Yin; Wang, Jin; Huang, Zheng;
Ding, Fuxin; Yuan, Naiju

CORPORATE SOURCE: Department of Chemical Engineering, Tsinghua
University, Beijing, 100084, Peop. Rep. China

SOURCE: Tsinghua Science and Technology (1996), 1(4),
336-340

CODEN: TSTEF7; ISSN: 1007-0214

PUBLISHER: Editorial Board of Journal of Tsinghua
University

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Protein mixts. are sepd. by multichannel flow electrophoresis (MFE) in a 5-compartment electrolyzer partitioned by membranes. Polyvinyl alc. (PVA), polyethylene glycol 4000 (PEG 4000) and polyvinylpyrrolidone K30 (PVP K30) were applied to the MFE as

shielding polymers to prevent protein adsorption on the polysulfone microfiltration membrane during the electrophoresis process. The effects of polymer concn. on the protein transmembrane flux were examd. It was found that PVA, PEG 4000 and PVP K30 greatly reduced protein adsorption on the membrane surface. However, their influences on protein migration in an elec. field were different. Continuous sepn. of bovine serum albumin and **Hb** mixt. was conducted using PEG 4000 as a shielding polymer and yielded 46.6 mg BSA and 25.7 mg HBB per h. These results show a high potential for scaling MFE up to large scale sepn. and purifn. of biomols.

IT 25322-68-3, Polyethylene glycol

RL: ARU (Analytical role, unclassified); ANST (Analytical study) (application of hydrophilic polymers in multichannel flow electrophoresis)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 7 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:536067 HCAPLUS

DOCUMENT NUMBER: 127:185584

TITLE: The impact of polyethylene glycol conjugation on bovine **hemoglobin's** circulatory half-life and renal effects in a rabbit top-loaded transfusion model

AUTHOR(S): Conover, Charles D.; Gilbert, Carl W.; Shum, Kwok L.; Shorr, Robert G. L.

CORPORATE SOURCE: Research and Development, Formulations-Toxicology Department, Enzon Inc., Piscataway, NJ, 08854, USA

SOURCE: Artificial Organs (1997), 21(8), 907-915
CODEN: ARORD7; ISSN: 0160-564X

PUBLISHER: Blackwell

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This study compares the effects of polyethylene glycol (PEG) modified bovine **Hb** on vascular half-life and renal function in rabbits to those of unmodified bovine **Hb**. Renal function was assessed by the measurement of the glomerular **filtration** rate, urinalysis, blood chemistries, **Hb** excretion rates, and tissue histol. The influence of infusion rates on **Hb** excretion rates and organ morphol. was also examd. The mean half-life of unmodified bovine **Hb** was 3.0 h, which was extended 14-fold to 43.2 h following PEG conjugation. The glomerular **filtration** rate, urinalysis, and blood chemistries were not greatly affected by either the unmodified bovine **Hb** or the PEG modified bovine **Hb**. However, unmodified bovine **Hb** did demonstrate significant hemoglobinuria (**Hb** excretion levels in excess of 1.0% of the infused dose at all infusion rates given) while PEG modified bovine **Hb** did not. In addn., histol. examn. by light microscopy indicated that the most severe morphol. changes occurred in animals that received unmodified bovine **Hb**. This data suggests that PEG modification of bovine **Hb** significantly reduced some of the adverse effects of bovine **Hb** on renal physiol. and morphol.

IT 25322-68-3, Polyethylene glycol

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(enhanced half-life and reduced kidney toxicity of polyethylene glycol-modified **Hb**)

L20 ANSWER 8 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:442351 HCAPLUS

DOCUMENT NUMBER: 127:173367

TITLE: Continuous separation of proteins by hydrophilic polymer shielded multichannel flow electrophoresis

AUTHOR(S): Liu, Zheng; Zhao, Yin; Shen, Zhongyao; Ding, Fuxin; Yuan, Naiju

CORPORATE SOURCE: Department of Chemical Engineering, Tsinghua University, Beijing, 100084, Peop. Rep. China

SOURCE: Chinese Journal of Chemical Engineering (1997), 5(2), 141-146

CODEN: CJCEEB; ISSN: 1004-9541

PUBLISHER: Chemical Industry Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Continuous sepn. of protein mixts. by multichannel flow electrophoresis (MFE) was carried out in a 5-compartment electrolyzer partitioned by membranes. Polyvinyl alc. (PVA), polyethylene glycol 4000 (PEG 4000) and polyvinylpyrrolidone K30 (PVP K30) were applied to the MFE as shielding polymers to prevent protein adsorption on the polyethersulfone microfiltration membrane, which was used to space the central compartment and the elution compartments, during the electrophoresis process. The effects of polymer concn. on protein transmembrane flux were examd. It was found that PVA, PEG 4000 and PVP K30 greatly reduced protein adsorption on the membrane surface. Continuous sepns. of bovine serum albumin (BSA) and **Hb** (HBB) mixt. in the presence of PEG 4000 yielded 26.6mg BSA 40.4mg HBB per h. These results have shown a high potential of scaling up MFE for large scale sepn. and purifn. of biomols.

IT 25322-68-3

RL: NUU (Other use, unclassified); USES (Uses)

(continuous sepn. of proteins by hydrophilic polymer shielded multichannel flow electrophoresis)

L20 ANSWER 9 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:393377 HCAPLUS

DOCUMENT NUMBER: 127:86186

TITLE: Detection of residual polyethylene glycol derivatives in pyridoxylated-hemoglobin -polyoxyethylene conjugate

AUTHOR(S): Miles, Paul J.; Langley, Kate V.; Stacey, Cyrus J.; Talarico, Todd L.

CORPORATE SOURCE: Apex Bioscience, Inc., Research Triangle Park, NC, 27709, USA

SOURCE: Artificial Cells, Blood Substitutes, and Immobilization Biotechnology (1997), 25(3), 315-326

CODEN: ABSBE4; ISSN: 1073-1199

PUBLISHER: Dekker

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Purified **Hb** solns. have been shown to cause renal toxicity in animals. Safe use of **Hb** based therapeutics in humans

requires modification of the **Hb** mol. to prevent this toxicity. **Hb** modification may be accomplished by crosslinking the dimers within the **Hb** tetramer or by derivatization of the .alpha. and/or .beta. subunits such that their size and/or charge prevents **filtration** by the glomeruli. Pyridoxylated **Hb polyoxyethylene** conjugate (PHP) consists of **Hb** mols. modified with .alpha.-**carboxymethyl**, .omega.-carboxymethoxy **polyoxyethylene** (POE). We have developed a high performance liq. chromatog.-based (HPLC) method which can quantitate residual POE at levels of 0.1 mg/mL or greater. The detection of POE at this level of sensitivity requires the use of an evaporative light scattering detector (ELSD). A differential refractometer may also be used for POE detection, however the limit of quantitation for this detector is approx. 10 fold greater than that obsd. for the evaporative light scattering detector, resulting in a redn. in sensitivity. The successful use of this method requires sample deproteinization using trichloroacetic acid. The reliability of the method has been demonstrated by spike recovery, precision, and reproducibility studies in PHP and buffer solns.

IT 25322-68-3, Polyethylene glycol
 RL: ANT (Analyte); ANST (Analytical study)
 (detection of residual polyethylene glycol derivs. in
 pyridoxylated-**Hb**-polyoxyethylene conjugate)

L20 ANSWER 10 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:305709 HCAPLUS

DOCUMENT NUMBER: 127:15033

TITLE: Hydrophilic polymer enhanced multichannel flow electrophoresis

AUTHOR(S): Liu, Zheng; Zhao, Yin; Shen, Zhongyao; Ding, Fuxin; Yuan, Naiju

CORPORATE SOURCE: Department of Chemical Engineering, Tsinghua University, Beijing, 100084, Peop. Rep. China

SOURCE: Separation Science and Technology (1997), 32(7), 1303-1313

CODEN: SSTEDS; ISSN: 0149-6395

PUBLISHER: Dekker

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Two kinds of polysulfone microfiltration membranes were applied to the multicompartament electrolyzer of multichannel flow electrophoresis (MFE) to increase MFE output. Liq.-membrane interface modification aimed at reducing protein adsorption on the membrane surface was studied by addn. of polyvinyl alc., polyethylene glycol 4000, and polyvinylpyrrolidone K30 in the protein soln. The exptl. results show that the presence of these polymers reduces the protein adsorption, and the electrophoretic migration speed of the charged protein in the membrane is dominated by the interaction between the protein and the membrane. Continuous sepn. of a bovine serum albumin and **Hb** mixt. in the presence of PEG 4000 was conducted in a HT Tuffryn-and a Supor-spaced MFE electrolyzer resp., and yielded over 67 mg protein product per h. The protein product fluxes were stable throughout the running period.

IT 25322-68-3

RL: NUU (Other use, unclassified); PEP (Physical, engineering or chemical process); PROC (Process); USES (Uses)

PCT/26515

(hydrophilic polymer-enhanced multichannel flow electrophoresis)

L20 ANSWER 11 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:85572 HCAPLUS

DOCUMENT NUMBER: 126:162268

TITLE: Method for preparing storage stable colloids

INVENTOR(S): Quay, Steven C.

PATENT ASSIGNEE(S): Sonus Pharmaceuticals, USA

SOURCE: U.S., 28 pp., Cont.-in-part of U.S. Ser. No. 8,172.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-------------|--|----------|-----------------|----------|
| US 5595723 | A | 19970121 | US 1993-148284 | 19931108 |
| US 5558855 | A | 19960924 | US 1993-8172 | 19930125 |
| IN 175599 | A | 19950715 | IN 1993-CA232 | 19930422 |
| CA 2154590 | AA | 19940804 | CA 1994-2154590 | 19940119 |
| WO 9416739 | A1 | 19940804 | WO 1994-US422 | 19940119 |
| W: | AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN | | | |
| RW: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | |
| AU 9461624 | A1 | 19940815 | AU 1994-61624 | 19940119 |
| AU 680652 | B2 | 19970807 | | |
| EP 680341 | A1 | 19951108 | EP 1994-908587 | 19940119 |
| EP 680341 | B1 | 20010509 | | |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | |
| BR 9405667 | A | 19951121 | BR 1994-5667 | 19940119 |
| CN 1119831 | A | 19960403 | CN 1994-191564 | 19940119 |
| CN 1068230 | B | 20010711 | | |
| HU 72323 | A2 | 19960429 | HU 1995-2163 | 19940119 |
| JP 08508977 | T2 | 19960924 | JP 1994-517084 | 19940119 |
| US 5558853 | A | 19960924 | US 1994-182024 | 19940119 |
| PL 176116 | B1 | 19990430 | PL 1994-309986 | 19940119 |
| PL 176870 | B1 | 19990831 | PL 1994-325737 | 19940119 |
| EP 1038535 | A2 | 20000927 | EP 2000-109817 | 19940119 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE | | | |
| SK 281535 | B6 | 20010409 | SK 1995-930 | 19940119 |
| AT 200985 | E | 20010515 | AT 1994-908587 | 19940119 |
| ES 2158892 | T3 | 20010916 | ES 1994-908587 | 19940119 |
| IL 108416 | A1 | 19981030 | IL 1994-108416 | 19940124 |
| ZA 9400508 | A | 19940905 | ZA 1994-508 | 19940125 |
| NO 9502819 | A | 19950922 | NO 1995-2819 | 19950717 |
| FI 9503546 | A | 19950922 | FI 1995-3546 | 19950724 |
| AU 9745091 | A1 | 19980205 | AU 1997-45091 | 19971110 |
| AU 710508 | B2 | 19990923 | | |

PRIORITY APPLN. INFO.:

| | | |
|----------------|----|----------|
| US 1993-8172 | A2 | 19930125 |
| US 1993-148284 | A | 19931108 |
| EP 1994-908587 | A3 | 19940119 |
| US 1994-182024 | A | 19940119 |

Searcher : Shears 308-4994

WO 1994-US422 W 19940119

AB Agents for enhancing the contrast in a diagnostic ultrasound procedure comprise colloidal dispersions of the liq.-in-liq. type, i.e., emulsions or microemulsions, in which the dispersed liq. phase is a high vapor pressure chem. which undergoes a phase change from a dispersed liq. to a highly echogenic dispersed gaseous foam or spherical foam following administration to an organism. The liq. state of the dispersed phase allows one to manuf. extremely stable, pharmaceutically acceptable emulsions with particle sizes typically below 1000 nm. The gaseous state at body temp. yields highly echogenic microbubbles, typically below 10,000 nm in diam., which are effective as ultrasound contrast agents. I.v., intraarterial, oral, i.p., and intrauterine dosage forms, methods of administration, and imaging techniques are described. A preferred method of prepg. a storage-stable ultrasound contrast agent comprises the steps of: (a) mixing a surfactant with water to form an aq. continuous phase, (b) adding a fluorine-contg. compd. in gas form to the aq. continuous phase, wherein the compd. has a b.p. $\leq 37^\circ\text{C}$ and is selected from the group consisting of aliph. hydrocarbons, org. halides and ethers having six or fewer carbon atoms, and (c) forming a liq. in liq. colloidal dispersion by condensing the gas in the aq. continuous phase. A soln. contg. sucrose, Pluronic P123, and Zonyl FSO was sonicated and mixed with dodecafluoropentane. The suspension was passed through a microfluidizer and then a 0.22 μm filter to give a stable colloidal dispersion.

IT 25322-68-3

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(colloidal dispersions stabilized by amphiphilic agents for enhancing contrast in diagnostic ultrasound procedure)

L20 ANSWER 12 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:69114 HCAPLUS

DOCUMENT NUMBER: 126:176747

TITLE: Effect of surface-modification of
hemoglobin-vesicles (HbV) with
polyethyleneglycol-lipid or glycolipid

AUTHOR(S): Park, Sung Ick; Sou, Keitarou; Sakai, Hiromi;
Takeoka, Shinji; Nishide, Hiroyuki; Tsuchida,
Eishun

CORPORATE SOURCE: Adv. Res. Cent. Sci. Eng., Waseda Univ., Tokyo,
169, Japan

SOURCE: Jinko Ketsueki (1996), 4(1), 9-13

CODEN: JIKEFK; ISSN: 1341-1594

PUBLISHER: Nippon Ketsueki Daitaibutsu Gakkai

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB HbV which encapsulate a purified and concd. Hb soln. with lipid bilayer membranes were studied as oxygen-carrying particles with good rheol. properties. When solns. of polyethylene glycol (PEG)-lipid or glycolipid conjugating a maltopentaose were added to the HbV suspension, the lipids were spontaneously incorporated into the outer surface of the HbV, and modified the surface with PEG chains or oligosaccharide chains. Aggregation of the unmodified HbV when suspended in an 5 wt.-%-albumin soln. at the Hb concn. of 10 g/dL was suppressed by the modification with PEG. The unmodified HbV tends to aggregate in the albumin soln. and incre. the soln. viscosity esp. at low shear rates. While, the

modification effectively reduces the viscosity because of the suppression of the aggregation. Permeability of HbV through membrane **filters** having penetrated pores with a regulated size was examd. in relation with the degree of aggregation during a capillary flow. Both the unmodified and modified HbV have the higher permeability than blood and lower than stroma-free **Hb** soln. at the same **Hb** concn. (10 g/dL). PEG-HbV and glyco-HbV showed higher permeability than the unmodified HbV. Thus, the soln. properties of the HbV were improved by the surface modification and excellent behaviors in microcirculation would be expected.

IT 25322-68-3D, PEG, phospholipid conjugates

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(surface modification of **Hb**-vesicles with polyethylene glycol-lipid or glycolipid)

L20 ANSWER 13 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:467217 HCAPLUS

DOCUMENT NUMBER: 125:137244

TITLE: Gels for encapsulation of biological materials

INVENTOR(S): Hubbell, Jeffrey A.; Pathak, Chandrashekhar P.;
Sawhney, Amarpreet S.; Desai, Neil P.; Hossainy,
Syed F. A.

PATENT ASSIGNEE(S): University of Texas System, USA

SOURCE: U.S., 34 pp., Cont.-in-part of U.S. Ser. No.
870, 540.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 12

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| US 5529914 | A | 19960625 | US 1992-958870 | 19921007 |
| US 5232984 | A | 19930803 | US 1991-740632 | 19910805 |
| US 5380536 | A | 19950110 | US 1991-740703 | 19910805 |
| WO 9316687 | A1 | 19930902 | WO 1993-US1776 | 19930301 |
| W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| AU 9337809 | A1 | 19930913 | AU 1993-37809 | 19930301 |
| AU 683209 | B2 | 19971106 | | |
| EP 627912 | A1 | 19941214 | EP 1993-907078 | 19930301 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| JP 07506961 | T2 | 19950803 | JP 1993-515100 | 19930301 |
| JP 3011767 | B2 | 20000221 | | |
| US 5573934 | A | 19961112 | US 1993-24657 | 19930301 |
| BR 9306041 | A | 19971118 | BR 1993-6041 | 19930301 |
| CA 2117584 | C | 19980922 | CA 1993-2117584 | 19930301 |
| US 5858746 | A | 19990112 | US 1995-377911 | 19950125 |
| US 5834274 | A | 19981110 | US 1995-467693 | 19950606 |
| US 5843743 | A | 19981201 | US 1995-467815 | 19950606 |
| US 5801033 | A | 19980901 | US 1995-480678 | 19950607 |
| US 6258870 | B1 | 20010710 | US 1997-783387 | 19970113 |
| US 6231892 | B1 | 20010515 | US 1997-969910 | 19971113 |

| | | | | |
|------------------------|----|----------|----------------|-------------|
| US 6465001 | B1 | 20021015 | US 1998-33871 | 19980303 |
| US 2002058318 | A1 | 20020516 | US 2001-811901 | 20010319 |
| PRIORITY APPLN. INFO.: | | | US 1990-598880 | B2 19901015 |
| | | | US 1991-740632 | A3 19910805 |
| | | | US 1991-740703 | A2 19910805 |
| | | | US 1992-843485 | B2 19920228 |
| | | | US 1992-870540 | A2 19920420 |
| | | | US 1992-958870 | A 19921007 |
| | | | US 1993-24657 | A1 19930301 |
| | | | WO 1993-US1776 | A 19930301 |
| | | | US 1994-232054 | A3 19940428 |
| | | | US 1994-336393 | A3 19941110 |
| | | | US 1995-467693 | A1 19950606 |
| | | | US 1995-475175 | A2 19950607 |
| | | | US 1995-484160 | B3 19950607 |
| | | | US 1997-783387 | A1 19970113 |

AB This invention provides novel methods for the formation of biocompatible membranes around biol. materials using photopolymn. of water-sol. mols. The membranes can be used as a covering to encapsulate biol. materials or biomedical devices, as a 'glue' to cause >1 biol. substance to adhere together, or as carriers for biol. active species. Several methods for forming these membranes are provided. Each of these methods utilizes a polymn. system contg. water-sol. macromers, species which are at once polymers and macromols. capable of further polymn. The macromers are polymd. by using a photoinitiator (such as a dye), optionally a cocatalyst, optionally an accelerator, and radiation in the form of visible or long-wavelength UV light. The reaction occurs either by suspension polymn. or by interfacial polymn. The polymer membrane can be formed directly on the surface of the biol. material, or it can be formed on material which is already encapsulated.

IT 25322-68-3

RL: BUU (Biological use, unclassified); NUU (Other use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(gels for encapsulation of biol. materials)

L20 ANSWER 14 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1994:644903 HCAPLUS

DOCUMENT NUMBER: 121:244903

TITLE: Hemoglobinuria in rats: a sensitive test of renal **filtering** and absorption of PEG-hemoglobin, a red blood cell substitute.

AUTHOR(S): Gilbert, C.; Nho, K.; Johnson, M.; Linberg, R.; Shorr, R.

CORPORATE SOURCE: Enzon, Inc., Piscataway, NJ, 08854, USA

SOURCE: Artificial Cells, Blood Substitutes, and Immobilization Biotechnology (1994), 22(3), 535-41

CODEN: ABSBE4; ISSN: 1073-1199

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Hemoglobinuria, defined as **Hb** or **Hb** subunits in the urine, is an easily monitored, sensitive indicator of renal handling of **Hb**-based blood substitutes. **Hb** tetramer disocn. increases **filtration** by the kidneys. When the rate of **filtration** exceeds resorption, hemoglobinuria occurs. This study investigates the renal

filtration and absorption of polyethylene glycol-modified bovine **Hb** by monitoring for hemoglobinuria in several model systems.

IT **25322-68-3**, Polyethylene glycol
 RL: BPR (Biological process); BSU (Biological study, unclassified);
 BIOL (Biological study); PROC (Process)
 (**Hbs** modified with; hemoglobinuria in rats as sensitive
 test of renal **filtering** and absorption of PEG-
Hb)

L20 ANSWER 15 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1994:129046 HCAPLUS

DOCUMENT NUMBER: 120:129046

TITLE: Process for **hemoglobin** extraction and
 purification

INVENTOR(S): Shorr, Robert G. L.; Nho, Kwang; Cho, Myung Ok
 P.; Lee, Chyi; Czuba, Barbara; Shankar,
 Hariharan

PATENT ASSIGNEE(S): Enzon, Inc., USA

SOURCE: U.S., 11 pp.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| US 5264555 | A | 19931123 | US 1992-913138 | 19920714 |
| WO 9401452 | A1 | 19940120 | WO 1993-US5789 | 19930617 |
| W: AU, BR, CA, FI, HU, JP, KR, NO, NZ, PL, RO, RU, SE, SK, UA | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| AU 9346383 | A1 | 19940131 | AU 1993-46383 | 19930617 |
| EP 654039 | A1 | 19950524 | EP 1993-916583 | 19930617 |
| EP 654039 | B1 | 20000920 | | |
| R: CH, DE, DK, FR, GB, IE, LI, NL | | | | |

PRIORITY APPLN. INFO.: US 1992-913138 A 19920714
 WO 1993-US5789 A 19930617

AB Methods are disclosed for sepg. **Hb** from erythrocytes by contacting erythrocytes with a hypotonic buffer soln. at a rate sufficient to render the release of **Hb** from said erythrocytes without significant lysis. The **Hb** is then sepd. from the erythrocytes. Methods are also disclosed for purifying **Hb** solns. of DNA, endotoxins and phospholipids by contacting the **Hb** solns. with an anion exchange medium. Thus, concd. bovine erythrocytes were prefiltered and then dild. under continuous mixing with a hypotonic buffer contg. NaCl 80, KCl 1.8, K₂HPO₄ 1.33, and KH₂PO₄ 5.33 mM (pH 7.3-7.5). The **Hb** was extd. from the soln. by recirculation through a hollo-fiber cartridge. The isolated **Hb** was delipidated using a column of WP-PEI or QMA-Spherosil M.

IT **25322-68-3D**, Polyethylene glycol, **Hb** conjugates
 RL: ANST (Analytical study)
 (for blood substitute, **Hb** purifn. from endotoxin and
 phospholipid for, anion exchange chromatog. in)

L20 ANSWER 16 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1993:420160 HCAPLUS
DOCUMENT NUMBER: 119:20160
TITLE: Renal effects of multiple infusion of
pyridoxalated-hemoglobin
-polyoxyethylene conjugate (PHP) solution in
dogs
AUTHOR(S): Takahashi, Tsuyoshi; Iwasaki, Keiji; Malchesky,
Paul S.; Harasaki, Hiroaki; Matsushita,
Michiaki; Nose, Yukihiro; Rolin, Henry, III;
Hall, Philip M.
CORPORATE SOURCE: Dep. Artif. Organs, Cleveland Clin. Found.,
Cleveland, OH, USA
SOURCE: Artificial Organs (1993), 17(3), 153-63
CODEN: ARORD7; ISSN: 0160-564X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Pyridoxalated-Hb-polyoxyethylene conjugate (PHP), which is
made from out-dated human red blood cells by two major chem.
modifications, namely pyridoxalation and conjugation with
polyoxyethylene (POE), is currently under development as a physiol.
oxygen carrier. This study assessed the effects of PHP-88 soln.,
which contains 8% (wt/vol) each of Hb and maltose, on
renal function when it was infused 3 times every other day into the
intact circulation of 8 dogs (5 dogs for the PHP group and 3 for the
control group; 20 mL/kg for the first infusion, and 10 mL/kg each
for the second and third infusions, at the rate of 2.5 mL/h/kg).
Serial detns. of glomerular **filtration** rate (GFR) and
renal plasma flow (RPF) were carried out pre- and postinfusion for
up to 3 mo along with measurements of blood and urine analyses,
urine output rate, fractional excretion of sodium (FES), and free
water clearance (CH2O). The results showed that plasma colloid
osmotic pressure (COP) elevated at an av. of 3.3 mm Hg ($p = 0.0085$),
and GFR and RPF tended to increase by 13% (NS) and 38% (NS), resp.,
immediately after the third infusion with PHP soln. Urine output
rate increased during and after the infusion, and FES and CH2O also
increased for 24 h after the infusion in both groups. Blood urea
nitrogen, serum creatinine, and serum Na⁺ concns. were not affected
greatly by the infusions, but hematocrit was decreased by 8% in the
PHP group, indicating approx. a 42% expansion of plasma vol. These
changes were obsd. to return to their preinfusion levels by 1 wk
postinfusion. Renal histol. of the PHP group obtained at 2 wk
postinfusion revealed vacuole formation in the proximal tubules
which was not assocd. with any pathol. changes indicative of cell
death or regeneration. In 4 out of 5 dogs at 3 mo postinfusion
(necropsy), the vacuoles were not present. Though urinary N-acetyl
.beta.-glucosaminidase (NAG) activity had significantly increased
after infusion, it returned to the preinfusion level by 1 mo
postinfusion. No detrimental effect of vacuoles on the assessed
renal tubular functions was confirmed in the present study. The
results demonstrated that multiple infusions of PHP solns. were well
tolerated in normal dogs, and the obsd. effects were conceived
predominantly attributable to the physiol. response of the kidneys
to an oncotic load into the circulation, which produced plasma vol.
expansion.
IT 25322-68-3D, reaction products with pyridoxylated Hb
RL: BIOL (Biological study)
(renal effects of multiple infusion of)

L20 ANSWER 17 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1992:456653 HCAPLUS

DOCUMENT NUMBER: 117:56653

TITLE: Theories and experiments on nonisothermal matter transport in porous membranes

AUTHOR(S): Gaeta, F. S.; Ascolese, E.; Bencivenga, U.; Ortiz de Zarate, J. M.; Pagliuca, N.; Perna, G.; Rossi, S.; Mita, D. G.

CORPORATE SOURCE: Int. Inst. Genet. Biophys., CNR, Naples, 80125, Italy

SOURCE: Journal of Physical Chemistry (1992), 96(15), 6342-54

CODEN: JPCHAX; ISSN: 0022-3654

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The growing body of exptl. evidence on nonisothermal matter transport in artificial porous membranes until now has been interpreted alternatively within the frame of ref. of 1 of 3 independent theor. approaches. According to one, the force driving transport is due to transfer of momentum from thermal excitations to the medium; another assumes this force to be due to transported entropy balance; the third envisages distn. in vapor-filled pores as the particular transport mechanism occurring in hydrophobic membranes. Two of these approaches apply to both hydrophilic and hydrophobic membranes; the other is specific to the case of porous hydrophobic **filters** and to liqs. that cannot permeate them. The 2 general approaches are complementary, one constituting the thermodyn. representation of a phys. process that the other describes in terms of statistical mechanics; the third is incompatible with the other 2. The predictions of the alternative models diverge in various ways. Expts. specially designed to investigate the conflicting forecasts were carried out by employing 2 polar solvents and using a new exptl. technique to investigate the behavior of solute fluxes. This article presents a preliminary report of the main exptl. results obtained so far and a discussion of their relevance to the theor. dispute among the different approaches. A preliminary report is made of the main exptl. results obtained so far and their relevance to the theor. dispute among the different approaches is discussed.

IT 25322-68-3, Polyethylene glycol

RL: PRP (Properties)

(transport of, in porous membranes under nonisothermal conditions)

L20 ANSWER 18 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1992:76334 HCAPLUS

DOCUMENT NUMBER: 116:76334

TITLE: Effects of single-dose infusion of pyridoxalated-hemoglobin-polyoxyethylene conjugate solution on canine renal function

AUTHOR(S): Takahashi, Tsuyoshi; Iwasaki, Keiji; Malchesky, Paul S.; Harasaki, Hiroaki; Emoto, Hideto; Goldcamp, James B.; Matsushita, Michiaki; Nose, Yukihiko; Rolin, Henry, III; Hall, Phillip

CORPORATE SOURCE: Dep. Biomed. Eng. Appl. Therapeut., Cleveland Clin. Found., Cleveland, OH, 44195-5132, USA

SOURCE: Artificial Organs (1991), 15(6), 462-73

CODEN: ARORD7; ISSN: 0160-564X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Pyridoxalated-Hb-polyoxyethylene conjugate (PHP) is an acellular oxygen-carrying red blood cell substitute made from outdated human red blood cells. This study assessed the effect of PHP on renal function when PHP was infused with a clin. relevant dosage. The results showed an elevation of plasma colloid osmotic pressure by an av. of 4.4 mm Hg immediately postinfusion with PHP soln. An av. 23% decrease in glomerular **filtration** rate, without notable changes in renal plasma flow immediately postinfusion, was obsd. in the PHP group; the value returned to the preinfusion level by 1 wk postinfusion. Increases in parameters such as urine output, fractional excretion of Na, and free water clearance, which were more pronounced in the PHP group, were obsd. for 24 h after the infusion in both groups. Light microscopic examn. of kidney specimens taken at 2 wk postinfusion revealed a slight degree of vacuole formation in approx. 80% of the proximal tubules in the PHP group. The tubules were devoid of typical pathol. features of acute renal failure, and the vacuoles did not cause any observable changes in the assessed tubular functions.

IT 25322-68-3D, conjugates with pyridoxalated Hb

RL: BIOL (Biological study)

(kidney function response to single-dose infusion of)

L20 ANSWER 19 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1991:235059 HCAPLUS

DOCUMENT NUMBER: 114:235059

TITLE: Very low temperature casting of controlled release microspheres

INVENTOR(S): Gombotz, Wayne R.; Healy, Michael S.; Brown, Larry R.

PATENT ASSIGNEE(S): Enzytech, Inc., USA

SOURCE: PCT Int. Appl., 28 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 9013780 | A1 | 19901115 | WO 1990-US2425 | 19900501 |
| W: AU, CA, JP | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE | | | | |
| US 5019400 | A | 19910528 | US 1989-346143 | 19890501 |
| CA 2030550 | AA | 19901102 | CA 1990-2030550 | 19900501 |
| AU 9055309 | A1 | 19901129 | AU 1990-55309 | 19900501 |
| AU 621751 | B2 | 19920319 | | |
| EP 424516 | A1 | 19910502 | EP 1990-907980 | 19900501 |
| EP 424516 | B1 | 19921209 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE | | | | |
| JP 03504389 | T2 | 19910926 | JP 1990-506874 | 19900501 |
| JP 07039338 | B4 | 19950501 | | |
| AT 83310 | E | 19921215 | AT 1990-907980 | 19900501 |
| ES 2037563 | T3 | 19930616 | ES 1990-907980 | 19900501 |
| PRIORITY APPLN. INFO.: | | | US 1989-346143 | 19890501 |
| | | | EP 1990-907980 | 19900501 |

WO 1990-US2425 19900501

AB Polymeric microspheres are prep'd. by (1) freezing droplets of solns. contg. polymers, biol. active agents, and solvents by atomizing the droplets into a freezing nonsolvent having a temp. below the f.p. of the soln., (2) thawing the solvent in the frozen droplets of the solns., and (3) extg. the solvent from the droplets into a liq. nonsolvent to form spherical polymeric microspheres. The polymers include both bioerodible and nonerodible polymers. The biol. active agents include proteins, polysaccharides, nucleic acids, lipids, steroids, and drugs. An advantage of this method is that surface-active agents are not required in most cases. Thus, superoxide dismutase (42 mg) was added to 3.36 mL CH₂Cl₂ soln. contg. 0.5% poly(L-lactic acid) and the mixt. was sonicated. The resulting mixt. was extruded through an ultrasonic nozzle that was placed over a frozen layer of EtOH covered by a layer of liq. N. The nozzle atomized the mixt. into droplets, which are frozen upon contacting the liq. N to form microspheres. The container was placed at -80.degree. to evap. N and melt EtOH and when the temp. reached -95.1.degree., the CH₂Cl₂ was extd. from the microspheres into the EtOH. After 3 days, the microspheres were **filtered** from the solvent and then dried in a vacuum desiccator. The obtained microspheres were round spheres having diam. of 30-50 .mu.m.

IT 25322-68-3, Polyethylene oxide
 RL: BIOL (Biological study)
 (pharmaceutical microspheres contg., manuf. of, low-temp. casting in)

L20 ANSWER 20 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1991:69107 HCAPLUS

DOCUMENT NUMBER: 114:69107

TITLE: Preparation and use of polymer-coated affinity supports for hemoperfusion

INVENTOR(S): Mazid, Abdul M.

PATENT ASSIGNEE(S): Chembiomed Ltd., Can.

SOURCE: Eur. Pat. Appl., 26 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| EP 371636 | A2 | 19900606 | EP 1989-311540 | 19891108 |
| EP 371636 | A3 | 19900718 | | |
| R: AT, BE, CH, DE, ES, FR, GB, IT, LI, LU, NL, SE | | | | |
| US 5240601 | A | 19930831 | US 1988-270950 | 19881109 |
| CA 2002310 | AA | 19900509 | CA 1989-2002310 | 19891106 |
| AU 8944510 | A1 | 19901101 | AU 1989-44510 | 19891108 |
| AU 625377 | B2 | 19920709 | | |
| JP 02257964 | A2 | 19901018 | JP 1989-292103 | 19891109 |
| JP 2746291 | B2 | 19980506 | | |
| US 5149425 | A | 19920922 | US 1991-679801 | 19910403 |
| JP 08117333 | A2 | 19960514 | JP 1995-208942 | 19950816 |
| JP 3081137 | B2 | 20000828 | | |

PRIORITY APPLN. INFO.: US 1988-270950 A 19881109

AB A method is provided for coating chromatog. particulate supports to

give a biocompatible outer layer of synthetic membrane-type film which prevents the release of fines but permits adsorption of components to an affinity ligand. The membrane-type coating has a pore size of $\approx 20 \text{ nm}$. The coating process is described. Thus, PEG-300 (pore-controlling component) was added to polystyrene in trichloroethylene, followed by addn. of a haptenized support comprising the 8-azidocarbonyloctyl deriv. of trisaccharide A conjugated to diatomite. Following evapn. of solvent, the matrix was wetted, washed, and dried. The polystyrene-coated matrix was relatively free of fines, as compared to controls. When different amts. of PEG-300 were added, 1% PEG-300 gave results superior to those in which higher (4 and 28%) amts. were used. There was little, if any, nonspecific adsorption of essential blood components (platelets, white and red blood cells, Hb) to the matrix. In a simulated hemoperfusion, very little or no changes in concn. were found for total protein, albumin, bilirubin, cholesterol, alk. phosphatase, or lactic dehydrogenase; antibody to A1 antigen was adsorbed by the affinity ligand.

IT 25322-68-3

RL: USES (Uses)

(as pore-controller, in hemoperfusion affinity matrix support with polymer coating)

IT 32131-17-2, Nylon-66, biological studies

RL: BIOL (Biological study)

(hemoperfusion affinity support coated with)

L20 ANSWER 21 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1990:94796 HCAPLUS

DOCUMENT NUMBER: 112:94796

TITLE: Chromatography based on membrane separation with vesicular packing material

AUTHOR(S): Ehwald, R.; Fuhr, G.; Olbrich, M.; Goering, H.; Knoesche, R.; Kleine, R.

CORPORATE SOURCE: Sekt. Biol., Humboldt Univ. Berlin, Berlin, 1040, Ger. Dem. Rep.

SOURCE: Chromatographia (1989), 28(11-12), 561-4
CODEN: CHRGB7; ISSN: 0009-5893

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A new vesicular packing material-prepd. from plant cell clusters by purifn. of the intact cell wall framework-is suitable for chromatog., giving high performance at low pressure gradients. The sepn. is achieved by dialysis through the cell wall, which is an ultrafilter membrane with an extremely sharp size limit of sepn. Almost the whole of the stationary liq. phase is located within the vesicle (empty cell) lumina. In contrast to gel **filtration**, vesicle chromatog. gives a practically ideal sepn. of 2 size groups with an extremely short fractionation range. The size limit of sepn. was investigated by chromatog. of proteins and other polymers. Group sepn. of mols. of a polydisperse dextran std. prepn. showed that the crit. Stokes' diam. for dextran permeation into the stationary liq. phase of the vesicular packing is 5-6 nm.

IT 25322-68-3, PEG

RL: ANST (Analytical study)

(sepn. of, by vesicle chromatog., membrane sepn. with vesicular packing material in)

L20 ANSWER 22 OF 37 HCAPLUS COPYRIGHT 2002 ACS

PCT/26515

ACCESSION NUMBER: 1989:601587 HCAPLUS
DOCUMENT NUMBER: 111:201587
TITLE: Hemoglobin modified with poly(alkylene oxide)
INVENTOR(S): Iwasaki, Keiji; Iwashita, Yuji; Okami, Taketoshi
PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan
SOURCE: Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-----------------------|------|----------|-----------------|----------|
| EP 206448 | A1 | 19861230 | EP 1986-301108 | 19860218 |
| EP 206448 | B1 | 19901114 | | |
| R: CH, DE, GB, IT, LI | | | | |
| US 4670417 | A | 19870602 | US 1986-831500 | 19860221 |
| JP 62089630 | A2 | 19870424 | JP 1986-142302 | 19860618 |
| JP 06076333 | B4 | 19940928 | | |

PRIORITY APPLN. INFO.: JP 1985-132056 19850619
AB Poly(alkylene oxide) is bonded to Hb by way of an amide group. The modified Hb has a high affinity to O and is stable. A soln. of poly(ethylene oxide) and Et 3-chloropropionate was treated with AgO and heated at 70.degree., for 24 h, followed by **filtration**. The **filtrate** was treated with Et2O and the ppt. formed was dissolved in water, followed by pH adjustment to 11 (NaOH). The soln. was kept overnight at 60.degree., adjusted to pH 5 (HCl) and subjected to solvent evapn. The residue was dissolved in CH2Cl2-Et2O (1:1), **filtered** and the **filtrate** concd. to give a ppt. The ppt. was dissolved in H2O and chromatographed on Bio-Rad AG/X2 (00.5N HCl elution). The product and N-hydroxysuccinimide were dissolved in DMF and dicyclohexylcarbodiimide was added to the soln., to give an activated poly(ethylene oxide) ester, which was treated with bovine Hb and L-lysine in 0.1M borate buffer to give the modified Hb.
IT 25322-68-3DP, Poly(ethylene oxide), Hb conjugates
RL: PREP (Preparation)
(prepn. of, as blood substitute)
IT 25322-68-3
RL: RCT (Reactant)
(reaction of, with Et chloropropionate)

L20 ANSWER 23 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1988:597118 HCAPLUS
DOCUMENT NUMBER: 109:197118
TITLE: Preparation of virus-free pyridoxylated hemoglobin from the blood of HBV or HTLV-I healthy carriers
AUTHOR(S): Sekiguchi, S.; Ito, K.; Kobayashi, M.; Ototake, N.; Kosuda, M.; Kwon, K. W.; Ikeda, H.
CORPORATE SOURCE: Res. Div., Hokkaido Red Cross Blood Cent., Sapporo, 064, Japan
SOURCE: Biomater., Artif. Cells, Artif. Organs (1988), 16(1-3), 113-21
CODEN: BACOEZ; ISSN: 0890-5533

Searcher : Shears 308-4994

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Pyridoxylated **Hb** (PLP-**Hb**), a possible substitute for red cells as an artificial oxygen carrier, was prepd. from outdated human blood. By conjugation with polyethylene glycol (PEG), the biol. half-life was increased about 3-fold at 82% blood replacement in rats without significant side effects in vivo or in vitro. For the prepn. of virus-free PEG-PLP-**Hb** from HBV or HTLV-I pos. blood, a considerable amt. of HBV (Dane particles) could be removed from HBV-pos. red cells by washing, and **filtration** through a porous cellulose **filter**, BMM-30, and HBV-DNA in the **filtered** fractions decreased to <0.33% of the initial amt. More than 96% of blood leukocytes could be removed with a leukocyte removal **filter**, Sepacell R-500. The leukocytes collected from **filtrated** fractions of HTLV-I pos. blood did not survive beyond 3 days. Since transmission of HTLV-I occurs by cell to cell contact and is rare in cell-free condition, it is unlikely that the PLP-**Hb** prepd. from HTLV-I pos. blood, which is deprived of leukocytes, transmits HTLV-I infection.

IT **25322-68-3DP**, Polyethylene glycol, conjugates with pyridoxylated **Hb**
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of virus-free, as blood substitutes)

L20 ANSWER 24 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1988:596976 HCAPLUS

DOCUMENT NUMBER: 109:196976

TITLE: A new resuscitation fluid "Stabilized **Hemoglobin**." Preparation and characteristics

AUTHOR(S): Iwashita, Y.; Yabuki, A.; Yamaji, K.; Iwasaki, K.; Okami, T.; Hirata, C.; Kosaka, K.

CORPORATE SOURCE: Ajinomoto Co., Inc., Kawasaki, Japan

SOURCE: Biomater., Artif. Cells, Artif. Organs (1988), 16(1-3), 271-80
 CODEN: BACOEZ; ISSN: 0890-5533

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A new oxygen carrier for use as a blood substitute was prepd. and characterized in vitro. Pyridoxalated **Hb**, which was obtained by the reaction of human **Hb** with pyridoxal-5-phosphate, was modified by **.alpha.-carboxymethyl-.omega.-carboxymethoxyl polyoxyethylene (POE)** of the mol. wt. 3600 daltons. To eliminate viruses and nucleic acids possibly contaminated, the **Hb** soln. was purified by ultrafiltration with a membrane of the nominal mol. wt. limit 300 kilodaltons. Furthermore POE conjugated pyridoxalated **Hb** was treated with 20% EtOH to inactivate viruses. A concn. of **Hb**, which is incorporated in the conjugate, of the final product was fixed at 6% to make normovolemic exchange transfusion possible. In consideration of the stability during transporting and storage, lyophilized product was selected as a final form (Stabilized **Hb**). Stabilized **Hb** could be stored in a refrigerator over 1 yr within the acceptable metHb increase (15%). Viscosity of Stabilized **Hb** soln. was detd. at 2.4 cP and is almost half of whole blood and therefore this will be useful not

only in resuscitation but also in improvement of microcirculation.

L20 ANSWER 25 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1988:451161 HCAPLUS

DOCUMENT NUMBER: 109:51161

TITLE: Studies on the physical state of water in living cells and model systems. VIII. Water vapor sorption on proteins and oxygen-containing polymers at physiological vapor pressures: presenting a new method for the study of vapor sorption at close to and including saturation

AUTHOR(S): Ling, G. N.; Hu, W. X.

CORPORATE SOURCE: Dep. Mol. Biol., Pennsylvania Hosp., Philadelphia, PA, 19107, USA

SOURCE: Physiol. Chem. Phys. Med. NMR (1987), 19(4), 251-69

CODEN: PCPNER; ISSN: 0748-6642

DOCUMENT TYPE: Journal

LANGUAGE: English

AB An extremely simple exptl. set-up, utilizing a Mason jar, **filter** paper, and a weighing cup, was designed for ascertaining the rate of gain or loss of water by a polymer soln. at different vapor pressures (using the null-point method). The percentage change in sample water content, over a 5-day period, was plotted vs. the water content of each sample. The null-point method was successfully applied to detn. of equil. water sorption of polymers at very high relative humidity as well as at lower vapor pressures. Sorption isotherms of polyethylene oxide, polyethylene glycol, polyvinylpyrrolidone, polyvinylmethyl ether, and gelatin at very high vapor pressures indicated very high water uptake. Comparable studies with **Hb**, albumin, and γ -globulin indicated a much lower water uptake. The physiol. implications were discussed.

IT 25322-68-3, Polyethylene glycol

RL: ANST (Analytical study)

(water vapor sorption on, at physiol. vapor pressures, detn. of)

L20 ANSWER 26 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1986:221637 HCAPLUS

DOCUMENT NUMBER: 104:221637

TITLE: New aspects in the use of polyvinyl alcohol in practical biochemistry

AUTHOR(S): Tretyakov, A. V.

CORPORATE SOURCE: Lab. Sravnitel. Biokhim. Krovi, Inst. Evol. Fiziol. Biokhim. im. Sechenova, Leningrad, USSR

SOURCE: Lab. Delo (1986), (4), 228-9

CODEN: LABDAZ; ISSN: 0023-6748

DOCUMENT TYPE: Journal

LANGUAGE: Russian

AB Poly(vinyl alc.) (I) was used for detn. of inorg. P by nephelometry and as a gel **filter** for desalting of **Hbs**. In the 1st case, I formed an insol. complex with ammonium molybdate and inorg. P (acid medium). A direct relation between inorg. P (KH_2PO_4) and turbidity was obsd. at 400 nm. The addn. of Tris or veronal (0.05M) had no substantial effect on the sensitivity. Secondly, a new gel **filter** was prepd. from I and polyethylene glycol (15,000). The gel **filter** has a high rate of **filtration** (500 mL/h). The gel column was prepd. from equal

wt. amts. of 2 polymers in pH 7.4 0.005M Tris-HCl. A good **filtration** rate is obsd. for 5-6 h, thereafter the rate decreases.

IT 25322-68-3

RL: ANST (Analytical study)
(as gel **filter** with polyvinyl alc., for **Hb**
purifn.)

L20 ANSWER 27 OF 37 HCAPLUS .COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1985:483832 HCAPLUS

DOCUMENT NUMBER: 103:83832

TITLE: Macromolecular conjugates to **hemoglobin**
and their use

PATENT ASSIGNEE(S): Braun, B., Melsungen A.-G., Fed. Rep. Ger.

SOURCE: Ger. Offen., 26 pp.

CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| DE 3340592 | A1 | 19850523 | DE 1983-3340592 | 19831110 |
| US 4698387 | A | 19871006 | US 1984-665354 | 19841026 |
| FI 8404331 | A | 19850511 | FI 1984-4331 | 19841105 |
| EP 142125 | A2 | 19850522 | EP 1984-113405 | 19841107 |
| EP 142125 | A3 | 19860528 | | |
| R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE | | | | |
| ES 537507 | A1 | 19860601 | ES 1984-537507 | 19841108 |
| DK 8405349 | A | 19850511 | DK 1984-5349 | 19841109 |
| NO 8404494 | A | 19850513 | NO 1984-4494 | 19841109 |
| JP 60123425 | A2 | 19850702 | JP 1984-237409 | 19841110 |
| PRIORITY APPLN. INFO.: | | | DE 1983-3340592 | 19831110 |

AB Macromol. conjugates to **Hb** composed of a physiol. inert polymer, an ionic ligand, and human **Hb** A in which the polymer is bound in a reversible and noncovalent manner to the allosteric center of **Hb** by the ligand are described. Thus, 1 g of lyophilized 3-bromo-2-hydroxypropyl dextran (BHP-Dextran) dissolved in a Na borate buffer was mixed with a 5 mM inositol hexaphosphate (IHP) soln. and allowed to stand at room temp. for 24 h. An aq. glycerin soln. (0.1M) was then added and the mixt. stirred for 10 h. The reaction product, IHP-BHP-Dextran, was **filtered** and lyophilized. An 18% **Hb** A soln. (pH 7.4) was deoxygenated and mixed with IHP-BHP-Dextran (1.0 g) and 5% glutardialdehyde, stirred for 30 min, and the product reduced by the addn. of NaBH₄. The reaction mixt. was **filtered** and adjusted to a 6% **Hb** conc. with 0.1M phosphate buffer (pH 7.4). The half satn. pressure of this prepn. was 47.9 mbar. These macromol. **Hb** conjugates can be used in medicine as auxiliary agents for blood compn. materials or blood plasma dilg. agents.

IT 25322-68-3DP, anionic ligand-**Hb** conjugates

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and medicinal uses of)

L20 ANSWER 28 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1985:200738 HCAPLUS

DOCUMENT NUMBER: 102:200738
 TITLE: Agent for use in detecting a substance in a body fluid
 INVENTOR(S): Kaminagayoshi, S.
 PATENT ASSIGNEE(S): Terumo Corp., Japan
 SOURCE: Belg., 21 pp.
 CODEN: BEXXAL
 DOCUMENT TYPE: Patent
 LANGUAGE: French
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-------------|------|----------|-----------------|----------|
| BE 900774 | A1 | 19850201 | BE 1984-213797 | 19841008 |
| JP 60086467 | A2 | 19850516 | JP 1983-194937 | 19831018 |
| JP 04029360 | B4 | 19920518 | | |
| EP 141244 | A1 | 19850515 | EP 1984-111426 | 19840925 |
| EP 141244 | B1 | 19881207 | | |

R: DE, FR, IT

PRIORITY APPLN. INFO.: JP 1983-194937 19831018

AB Color reagents are described to detect, with the aid of the reaction of a peroxidase or peroxidatively active substance, a hydroperoxide, H₂O₂, and other peroxides or to detect a peroxidase or peroxidatively active compd. itself. The reagents comprise a chromogen (e.g., benzidine deriv., phenol, etc.) that can be oxidized and change color as a result of O, the reaction of, e.g, a hydroperoxide, peroxidase, or a peroxidatively active substance as well as a chem. effective amt. of .gtoreq.1 oxidant such as NaIO₄, HIO₄, or metal salt. The reagents, which may be impregnated into **filter** paper or used in soln., are esp. useful for the detection of glucose or occult blood. Thus, for the detection of glucose in urine with a color test strip, **filter** paper was impregnated with a citrate buffer soln. contg. glucose oxidase, peroxidase, NaIO₄, and Na alginate, dried, then impregnated with a soln. contg. o-tolidine in Me₂CO, and dried. Glucose in urine (150 mg/dL) caused a color change in the paper even in the presence of ascorbic acid (50 mg). HIO₄ and CuSO₄ also could be used as oxidant.

IT 25322-68-3

RL: ANST (Analytical study)
 (color test strip contg., for occult blood detection)

L20 ANSWER 29 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1984:625804 HCAPLUS
 DOCUMENT NUMBER: 101:225804
 TITLE: Peroxidase activity detection composition
 INVENTOR(S): Wells, Henry John
 PATENT ASSIGNEE(S): Warner-Lambert Co. , USA
 SOURCE: Eur. Pat. Appl., 23 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|------|-----------------|------|
|------------|------|------|-----------------|------|

PCT/26515

| | | | | |
|---------------------------|----|----------|----------------|----------|
| EP 121317 | A1 | 19841010 | EP 1984-301219 | 19840224 |
| EP 121317 | B1 | 19880120 | | |
| EP 121317 | B2 | 19911127 | | |
| R: BE, DE, FR, GB, NL, SE | | | | |
| ZA 8401078 | A | 19840926 | ZA 1984-1078 | 19840214 |
| CA 1216215 | A1 | 19870106 | CA 1984-447379 | 19840214 |
| AU 8424710 | A1 | 19840906 | AU 1984-24710 | 19840217 |
| AU 557784 | B2 | 19870108 | | |
| BR 8400932 | A | 19841009 | BR 1984-932 | 19840228 |
| NO 8400767 | A | 19840903 | NO 1984-767 | 19840229 |
| NO 164202 | B | 19900528 | | |
| NO 164202 | C | 19900905 | | |
| JP 59166865 | A2 | 19840920 | JP 1984-36363 | 19840229 |
| | | | US 1983-471372 | 19830301 |

PRIORITY APPLN. INFO.:

AB A stable diagnostic compn. for detecting peroxidase (I) activity in various specimens is described; the mixt. which is composed of a sol. indicator material, an org. solvent, an oxidizing agent, and a buffer, can be used to detect I activity in fecal occult blood, **Hb**, and biol. fluids. Thus, 1 g of guaiac powder was dissolved in 100 mL of MeOH, and the soln. was **filtered** to remove undissolved particles. This soln. (50 mL) was mixed with 4.5 mL of 30% H₂O₂ followed by the addn. of 15 mL of 0.1M citrate buffer to adjust the pH to 5.0. H₂O (10 mL) and MeOH (25 mL) were successively added. The resultant soln. (100 mL) had a slight amber color. A drop of this compn. was applied to previously prepd. **Hb** specimens (drops of dild. blood samples on Whatman no. 1 **filter** paper), and a distinct change of color from colorless to blue was obsd. The **Hb** test procedure was repeated with the aforementioned soln. which had been stored at elevated temp. (45.degree.) for 6 wks. No appreciable loss of reactivity was obsd. Various org. solvents, H₂O-sol. indicators, and thickening agents may be used in the compn.

IT 25322-68-3

RL: BIOL (Biological study)
(in peroxidase detection in biol. fluids of human)

L20 ANSWER 30 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1984:598230 HCAPLUS

DOCUMENT NUMBER: 101:198230

TITLE: Polyalkylene glycol-bound **hemoglobins**
as blood substitutes

PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan; Fujirebio, Inc.

SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| ----- | ---- | ----- | ----- | ----- |
| JP 59104323 | A2 | 19840616 | JP 1982-214508 | 19821207 |
| AB Blood substitutes are prepd. by binding Hb to polyalkylene glycols in the absence of O. The Hb may be modified with pyridoxal derivs. prior to binding. Thus, 4 mL 10.9% human Hb soln. was dissolved in 18 mL 0.122 M Tris buffer (pH 6.8), and Ar gas was passed through the soln. throughout the process. Pyridoxal 5'-phosphate (6.6 mg) was then added, followed | | | | |

by 657 mg monomethoxypolyethylene glycol mono(succimidyl succinate) (av. mol. wt. 5000). The soln. was **filtered** to obtain 8.2 mL Hb complexes as blood substitutes.

IT **25322-68-3D, Hb complexes**
RL: BIOL (Biological study)
(as blood substitutes)

L20 ANSWER 31 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1984:486866 HCAPLUS

DOCUMENT NUMBER: 101:86866

TITLE: Calmodulin-binding proteins: visualization by 125I-calmodulin overlay on blots quenched with Tween 20 or bovine serum albumin and poly(ethylene oxide)

AUTHOR(S): Flanagan, Steven D.; Yost, Beverly

CORPORATE SOURCE: Div. Neurosci., Beckman Res. Inst. of the City of Hope, Duarte, CA, 91010, USA

SOURCE: Anal. Biochem. (1984), 140(2), 510-19
CODEN: ANBCA2; ISSN: 0003-2697

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To streamline detection of calmodulin-binding proteins, blotting techniques for the electrophoretic transfer of proteins onto nitrocellulose **filters** followed by overlay with 125I-calmodulin was adapted. Autoradiog. of the 125I-calmodulin-labeled blots allows the identification and quantitation of proteins that possess affinity for calmodulin. Five protocols for suppressing nonspecific binding and for enhancing specific interactions of 125I-calmodulin with electrophoretically sepd. proteins were investigated. Tween 20 and bovine serum albumin alone, as well as combinations of bovine serum albumin and poly(ethylene oxide) or Hb and gelatin, were evaluated as quenching and enhancing agents. Tween 20 proved highly effective for quenching nonspecific binding and for enhancing specific 125I-calmodulin binding of a 61,000-Mr rat brain protein, which was only faintly obsd. on blots quenched with proteins alone. However, Tween 20 dissocd. 50% of 68,000-Mr proteins and 80% of 21,000-Mr 125I-labeled protein stds. from the nitrocellulose **filter**. An alternative, the combination of bovine serum albumin followed by incubation with 15,000-20,000-Mr poly(ethylene oxide), proved satisfactory for the recovery of 61,000-Mr calmodulin-binding activity and for the detection of calmodulin-binding peptides (50,000-14,000 Mr) produced by limited proteolysis of rat brain 51,000-Mr calmodulin-binding protein. These blotting procedures for detection of calmodulin-binding proteins are compatible with a variety of 1-dimensional and 2-dimensional electrophoresis systems, including a 2-dimensional electrophoresis system utilizing urea and SDS in the 1st dimension and nonurea SDS electrophoresis in the 2nd, a system which proved useful for resolving calmodulin-binding proteins displaying anomalous electrophoretic migration in the presence of urea.

IT **25322-68-3**

RL: ANST (Analytical study)
(in detn. of calmodulin-binding proteins on gel blots)

L20 ANSWER 32 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1983:166880 HCAPLUS

DOCUMENT NUMBER: 98:166880

PCT/26515

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File 357:Derwent Biotech Res. 1982-2002/Jul W1

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Alert feature enhanced for multiple files, etc. See HELP ALERT.

File 113:European R&D Database 1997

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*File 113: This file is closed (no updates)

Set Items Description

| Set | Items | Description |
|-----|-------|---|
| S1 | 174 | APEG OR ACTIVAT?(W) (PEG OR POLYETHYLENE OR POLY(W)ETHYLENE- (W)GLYCOL |
| S2 | 86 | ALPHA(W) (CARBOXYMETHYL OR CARBOXY(W) (ME OR METHYL)) |
| S3 | 8 | S2(10N) (POLYOXYETHYLENE OR POLYOXY(W)ETHYLENE OR POLY(W) (O- XYETHYLENE OR OXY(W)ETHYLENE) OR CARBOXYMETHOXPOLYOXYETHYLENE OR METHOXPOLYOXYETHYLENE) |
| S4 | 21 | POE(S) (CARBOXYMETHYL? OR CARBOXY(W) (METHYL? OR ME)) |
| S5 | 15 | (S1 OR S3 OR S4) AND (HB OR HEMOGLOBIN OR HAEMOGLOBIN) |
| S6 | 13 | RD (unique items) |

>>>No matching display code(s) found in file(s): 65, 113

-Key term

6/3,AB/1 (Item 1 from file: 35)

DIALOG(R)File 35:Dissertation Abs Online

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732824 AAD8028393

B-CELL RESPONSES IN AUTOIMMUNE MICE: ANTIBODY PRODUCTION AND POLYCLONAL
ACTIVATION

Author: WOLOSCHAK, GAYLE E.

Degree: PH.D.

Year: 1980

Corporate Source/Institution: MEDICAL COLLEGE OF OHIO AT TOLEDO (0539)

Source: VOLUME 41/06-B OF DISSERTATION ABSTRACTS INTERNATIONAL.

PAGE 2117. 214 PAGES

Previous work has demonstrated the multifactorial nature of the autoimmune disease of NZB mice. Virologic, genetic, and immunologic components each contribute to this disease process. Recently, evidence has accumulated supporting a role for spontaneous polyclonal B-cell activation in self-reactivity. This study provides further evidence in support of B-cell activation as a factor contributing to the NZB autoimmune

manifestations.

NZB mice spontaneously produce autoantibodies to four erythrocyte (RBC) membrane antigens (X, HOL, *HB*, and I). Furthermore, recently developed autoimmune mouse strains, MRL and BXSB, have been shown by others to produce anti-X antibodies. This work extends those initial reports to include antibodies to HOL as well. HOL antigen could be detected on the surface of all mouse RBC tested including those from normal mouse strains. Exhaustive adsorption of NZB sera with RBC at either 25(DEGREES)C or 37(DEGREES)C totally eliminated anti-HOL antibody fluorescent staining. Erythrocytes were treated with the enzymes trypsin, hyaluronidase, collagenase, bromelain, and neuraminidase, and tested for the ability to bind to anti-HOL and anti-X antibodies. Collagenase could obliterate anti-HOL antibody binding to RBC without affecting anti-X antibody, suggesting that these are separate and distinct antigens, detectable by differing assay systems.

Another series of experiments was designed to determine whether B-cell activation of control strains of mice with lipopolysaccharide (LPS) could induce the same anti-erythrocyte antibody responses observed spontaneously in the NZB strain. When BALB/c and DBA/2 mice were injected intraperitoneally with 100 (mu)g of LPS, antibodies to X, HOL, and *HB* antigens could be detected two weeks later at levels comparable to those found spontaneously in NZB mice. Injection of C3H/HeJ mice, non-responders to LPS, resulted in no detectable anti-erythrocyte antibody responses. When NZB mice were treated with LPS in this way, serum levels of anti-RBC antibodies increased. A measure of the percent hemolysis induced by sera from these animals in the presence of an exogenous complement source revealed a higher incidence and hemolytic titer in LPS-injected BALB/c and DBA/2 strains than in PBS-injected mice. In addition, injection of LPS induced the appearance of erythrocyte-bound IgM and IgG in BALB/c, DBA/2, and NZB mice.

A cell fusion assay system was then devised as a means of measuring cell *activation*. *Polyethylene* *glycol* (PEG) was used to induce fusion between spleen cells of various mouse strains and the BW5147 thymoma cell line. A fusion index (FI) was calculated by determining the ratio of the number of nuclei in fused cells to the number of nuclei in all cells and multiplying by 100 (the FI could range from 0 to 100). Spleen cells from young and old BALB/c and NZB mice were compared in PEG-induced fusion assays. Results revealed low FI in BALB/c mice and high FI in NZB mice. BALB/c spleen cells stimulated with phytohemagglutinin, leucoagglutinin, concanavalin A, and LPS showed FI two to three fold higher than those found in unstimulated cultures, indicating that stimulated cells fuse at much higher rates. This response is mitogen dose-dependent. Treatment of NZB spleen cells with LPS, either in vivo by intraperitoneal injection or in vitro by culturing for five days, did not enhance FI when compared to untreated NZB splenocytes. This high FI of NZB spleen cells was insensitive to treatment with monoclonal anti-Thy-1.2 serum and complement, but was abrogated by treatment with anti-mouse immunoglobulin serum and complement. In addition, this spontaneously occurring high FI in NZB mice could be detected in animals as young as twelve days, but not in BALB/c animals of the same age. These experiments provide additional evidence in support of the hypothesis that polyclonal B-cell activation occurs spontaneously in NZB mice.

6/3,AB/2 (Item 1 from file: 144)
 DIALOG(R)File 144:Pascal
 (c) 2002 INIST/CNRS. All rts. reserv.

13046815 PASCAL No.: 97-0336475

Detection of residual polyethylene glycol derivatives in pyridoxylated-hemoglobin*-polyoxyethylene conjugate

MILES P J; LANGLEY K V; STACEY C J; TALARICO T L

Apex Bioscience, Inc., P.O. Box 12847, Research Triangle Park, NC 27709, United States

Journal: Artificial cells, blood substitutes, and immobilization biotechnology, 1997, 25 (3) 315-326

Language: English

Purified *hemoglobin* solutions have been shown to cause renal toxicity in animals. Safe use of *hemoglobin* based therapeutics in humans requires modification of the *hemoglobin* molecule to prevent this toxicity. *Hemoglobin* modification may be accomplished by crosslinking the dimers within the *hemoglobin* tetramer or by derivatization of the alpha and/or beta subunits such that their size and/or charge prevents filtration by the glomeruli. Pyridoxylated *hemoglobin* *polyoxyethylene* conjugate (PHP) consists of *hemoglobin* molecules modified with *alpha* -*carboxymethyl*, omega -carboxymethoxy *polyoxyethylene* (*POE*). We have developed a high performance liquid chromatography-based (HPLC) method which can quantitate residual *POE* at levels of 0.1 mg/ml or greater. The detection of *POE* at this level of sensitivity requires the use of an evaporative light scattering detector (ELSD). A differential refractometer may also be used for *POE* detection, however the limit of quantitation for this detector is approximately 10 fold greater than that observed for the evaporative light scattering detector, resulting in a reduction in sensitivity. The successful use of this method requires sample deproteinization using trichloroacetic acid. The reliability of the method has been demonstrated by spike recovery, precision, and reproducibility studies in PHP and buffer solutions.

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6/3,AB/3 (Item 1 from file: 440)

DIALOG(R)File 440:Current Contents Search(R)

(c) 2002 Inst for Sci Info. All rts. reserv.

03978128 References: 5

TITLE: RELATIONSHIP BETWEEN CHEMICAL PROPERTIES AND BIOLOGICAL PROPERTIES OF PYRIDOXALATED *HEMOGLOBIN*-POLYOXYETHYLENE

AUTHOR(S): IWASHITA Y

CORPORATE SOURCE: AJINOMOTO CO INC,CENT RES LABS,1-1

SUZUKICHO/KAWASAKI/KANAGAWA 210/JAPAN/ (Reprint)

PUBLICATION: BIOMATERIALS ARTIFICIAL CELLS AND IMMOBILIZATION BIOTECHNOLOGY, 1992, V20, N2-4, P299-307

GENUINE ARTICLE#: JM745

ISSN: 1055-7172

LANGUAGE: ENGLISH DOCUMENT TYPE: ARTICLE

ABSTRACT: Pyridoxalated *hemoglobin*-polyoxyethylene* (PHP) is a conjugate of human *hemoglobin* with *alpha*-carboxymethyl*, omega-carboxymethoxypolyoxyethylene*(*POE*). This conjugate is selected as an oxygen carrier for blood substitute because it can survive for a long time in the circulation and also it can transport the same amount of oxygen as red cell. Optimization of PHP has been done by changing the degree of the modification and reaction procedures in order to adjust viscosity and colloid osmotic pressure to physiological values.

The oxygen carrying capacity was physically evaluated by oxygen equilibrium curves and biologically by an ATP content in perfused isolated liver. Structural relationship of PHP to the binding properties to haptoglobin was studied and the effect of the POE modification on the binding properties was observed when the number of POE per one *hemoglobin* molecule is over six.

Based on the comparative study of solubility of met-PHP and met-SFH, the POE modification was suggested to reduce the toxicity of *hemoglobin* against organs.

Finally physical properties of PHP at low temperature was discussed in relation to organ preservation.

6/3,AB/4 (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
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01322386

Primers for synthesizing full length cDNA clones and their use
Primer zur Synthese von vollständigen cDNA Klonen und ihre Verwendung
Amorces pour la synthese de cADN de pleine longueur et leur utilisation
PATENT ASSIGNEE:

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292-0812, (JP), (Applicant designated States: all)

INVENTOR:

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Ishii, Shizuko, 4508-19-202, Yana, Kisarazu-shi, Chiba 292-0812, (JP)
Kawai, Yuri, 4508-19-201, Yana, Kisarazu-shi, Chiba 292-0812, (JP)
Wakamatsu, Ai, 1473-4-202, Takayanagi, Kisarazu-shi, Chiba 292-0014, (JP)
Sugiyama, Tomoyasu, 2-6-23-102, Kiyomidai, Kisarazu-shi, Chiba 292-0045,
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Nagai, Keiichi, 3-44-14-9-204, Sakuragaoka, Higashiyamato-shi, Tokyo
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Kojima, Shinichi, 2-7-10-202, Gion, Kisarazu-shi, Chiba 292-0052, (JP)
Otsuki, Tetsuji, 3-1-10-B102, Asahi, Kisarazu-shi, Chiba 292-0055, (JP)
Koga, Hisashi, 2-4-15, Asahi, Kisarazu-shi, Chiba 292-0055, (JP)

LEGAL REPRESENTATIVE:

VOSSIUS & PARTNER (100314), Siebertstrasse 4, 81675 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 1130094 A2 010905 (Basic)
EP 1130094 A3 011121

APPLICATION (CC, No, Date): EP 2000114089 000707;

PRIORITY (CC, No, Date): JP 99194486 990708; JP 2000118774 000111; JP
2000183765 000502

DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI;
LU; MC; NL; PT; SE

EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI

INTERNATIONAL PATENT CLASS: C12N-015/12; C12N-015/11; C12N-015/10;
C12N-015/70; C12N-015/85; C12N-005/10; C12N-001/21; C07K-014/47;
C07K-016/18; C12Q-001/68

ABSTRACT EP 1130094 A2

Primers for synthesizing full length cDNAs and their use are provided. 830 cDNA encoding a human protein has been isolated and nucleotide sequences of 5'-, and 3'-ends of the cDNA have been determined. Furthermore, primers for synthesizing the full length cDNA have been provided to clarify the function of the protein encoded by the cDNA. The full length cDNA of the present invention containing the translation start site provides information useful for analyzing the functions of the protein.

ABSTRACT WORD COUNT: 79

NOTE:

Figure number on first page: 1

LANGUAGE (Publication,Procedural,Application): English; English; English

FULLTEXT AVAILABILITY:

| Available Text | Language | Update | Word Count |
|------------------------------------|-----------|--------|------------|
| CLAIMS A | (English) | 200136 | 709 |
| SPEC A | (English) | 200136 | 97667 |
| Total word count - document A | | | 98376 |
| Total word count - document B | | | 0 |
| Total word count - documents A + B | | | 98376 |

6/3,AB/5 (Item 2 from file: 348)

DIALOG(R)File 348:EUROPEAN PATENTS

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01066190

IMPROVED INTERFERON POLYMER CONJUGATES

VERBESSEERTE INTERFERON-POLYMER KONJUGATE

CONJUGUES AMELIORES D'INTERFERON-POLYMERE

PATENT ASSIGNEE:

ENZON, INC., (1304434), 20 Kingsbridge Road, Piscataway, NJ 08854-3998,
(US), (Proprietor designated states: all)

INVENTOR:

GILBERT, Carl, W., 4655 Oakleigh Manor Drive, Powder Springs, GA 30127,
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PARK-CHO, Myung-Ok, 1-207 Dong, A Apt., Chang-dong, Tobong-gu, Seoul,
(KR)

LEGAL REPRESENTATIVE:

Ottevangers, Sietse Ulbe et al (20841), Vereenigde, Postbus 87930, 2508
DH Den Haag, (NL)

PATENT (CC, No, Kind, Date): EP 1039922 A1 001004 (Basic)
EP 1039922 B1 020612
WO 9932139 990701

APPLICATION (CC, No, Date): EP 98963947 981216; WO 98US26677 981216

PRIORITY (CC, No, Date): US 994622 971219

DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI;
LU; MC; NL; PT; SE

EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI

INTERNATIONAL PATENT CLASS: A61K-038/21; C07K-001/113; C07K-014/56;

A61P-035/00; A61P-031/12

NOTE:

No A-document published by EPO

LANGUAGE (Publication,Procedural,Application): English; English; English

FULLTEXT AVAILABILITY:

| Available Text | Language | Update | Word Count |
|----------------|----------|--------|------------|
|----------------|----------|--------|------------|

PCT/26515

| | | | |
|------------------------------------|-----------|--------|-------|
| CLAIMS B | (English) | 200224 | 873 |
| CLAIMS B | (German) | 200224 | 803 |
| CLAIMS B | (French) | 200224 | 1061 |
| SPEC B | (English) | 200224 | 7778 |
| Total word count - document A | | | 0 |
| Total word count - document B | | | 10515 |
| Total word count - documents A + B | | | 10515 |

6/3,AB/6 (Item 3 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
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00778408

CONJUGATES OF BDNF AND NT-3 WITH A WATER-SOLUBLE POLYMER
KONJUGATE BDNF UND NT-3 MIT EINEM WASSERLOSILICHEN POLYMER
CONJUGUES DU BDNF ET DU NT-3 ET D'UN POLYMERES HYDROSOLUBLE
PATENT ASSIGNEE:

AMGEN INC., (923233), Amgen Center, 1840 Dehavilland Drive, Thousand
Oaks, CA 91320-1789, (US), (applicant designated states:

AT;BE;CH;DE;DK;ES;FR;GB;GR;IE;IT;LI;LU;MC;NL;PT;SE)

INVENTOR:

KINSTLER, Olaf, F., 887 S. Charles Drive 21, Thousand Oaks, CA 91360,
(US)

YAN, Qiao, 1848 Marview Drive, Thousand Oaks, CA 91362, (US)

LEGAL REPRESENTATIVE:

Brown, John David et al (28811), FORRESTER & BOEHMERT

Franz-Joseph-Strasse 38, 80801 Munchen, (DE)

PATENT (CC, No, Kind, Date): EP 792288 A1 970903 (Basic)

EP 792288 B1 990120

WO 9615146 960523

APPLICATION (CC, No, Date): EP 95939123 951113; WO 95US14658 951113

PRIORITY (CC, No, Date): US 340131 941114

DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC;
NL; PT; SE

INTERNATIONAL PATENT CLASS: C07K-014/475; A61K-038/18;

NOTE:

No A-document published by EPO

LANGUAGE (Publication,Procedural,Application): English; English; English

FULLTEXT AVAILABILITY:

| Available Text | Language | Update | Word Count |
|------------------------------------|-----------|--------|------------|
| CLAIMS B | (English) | 9903 | 495 |
| CLAIMS B | (German) | 9903 | 471 |
| CLAIMS B | (French) | 9903 | 514 |
| SPEC B | (English) | 9903 | 7237 |
| Total word count - document A | | | 0 |
| Total word count - document B | | | 8717 |
| Total word count - documents A + B | | | 8717 |

6/3,AB/7 (Item 4 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
(c) 2002 European Patent Office. All rts. reserv.

00703327

IMPROVED INTERFERON POLYMER CONJUGATES
VERBESSERTE INTERFERON-POLYMERKONJUGATE
PRODUITS DE CONJUGAISON AMELIORES D'UN INTERFERON AVEC UN POLYMERES

Searcher : Shears 308-4994

PCT/26515

PATENT ASSIGNEE:

ENZON, INC., (1304433), 40 Kingsbridge Road, Piscataway, NJ 08854-3998,
(US), (Proprietor designated states: all)

INVENTOR:

GILBERT, Carl W., 26 Hampton Court, Basking Ridge, NJ 07920, (US)

CHO, Myung-Ok, 166A Cedar Lane, Highland Park, NJ 08901, (US)

LEGAL REPRESENTATIVE:

Smulders, Theodorus A.H.J., Ir. et al (21191), Vereenigde Postbus 87930,
2508 DH Den Haag, (NL)

PATENT (CC, No, Kind, Date): EP 730470 A1 960911 (Basic)

EP 730470 B1 020327

WO 9513090 950518

APPLICATION (CC, No, Date): EP 95902571 941110; WO 94US13207 941110

PRIORITY (CC, No, Date): US 150643 931110

DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC;
NL; PT; SE

INTERNATIONAL PATENT CLASS: A61K-038/21; C07K-001/08; C07K-001/10

NOTE:

No A-document published by EPO

LANGUAGE (Publication,Procedural,Application): English; English; English

FULLTEXT AVAILABILITY:

| Available Text | Language | Update | Word Count |
|----------------|----------|--------|------------|
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|----------|-----------|--------|-----|
| CLAIMS B | (English) | 200213 | 506 |
|----------|-----------|--------|-----|

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| CLAIMS B | (German) | 200213 | 462 |
|----------|----------|--------|-----|

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| CLAIMS B | (French) | 200213 | 596 |
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| SPEC B | (English) | 200213 | 3676 |
|--------|-----------|--------|------|

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| Total word count - document A | 0 |
|-------------------------------|---|

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| Total word count - document B | 5240 |
|-------------------------------|------|

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| Total word count - documents A + B | 5240 |
|------------------------------------|------|

6/3,AB/8 (Item 5 from file: 348)

DIALOG(R)File 348:EUROPEAN PATENTS

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00686989

Glycosaminoglycan-synthetic polymer conjugates.

Glukosominoglukan-synthetische-Polymer-Konjugaten.

Conjugues de glycosominoglucanes et de polymeres synthetiques.

PATENT ASSIGNEE:

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AT;BE;CH;DE;DK;ES;FR;GB;IT;LI;NL;SE)

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(DE)

PATENT (CC, No, Kind, Date): EP 656215 A1 950607 (Basic)

APPLICATION (CC, No, Date): EP 94117227 941101;

PRIORITY (CC, No, Date): US 146843 931103

DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; NL; SE

INTERNATIONAL PATENT CLASS: A61K-047/48; A61L-027/00; A61L-031/00;

ABSTRACT EP 656215 A1

Pharmaceutically acceptable, nonimmunogenic compositions are formed by
covalently binding glycosaminoglycans or derivatives thereof, to

hydrophilic synthetic polymers via specific types of chemical bonds to provide biocompatible conjugates. Useful glycosaminoglycans include hyaluronic acid, the chondroitin sulfates, keratan sulfate, chitin and heparin, each of which is chemically derivatized to react with a hydrophilic synthetic polymer. The conjugate comprising a glycosaminoglycan covalently bound to a hydrophilic synthetic polymer may be further bound to collagen to form a three component conjugate having different properties. The hydrophilic synthetic polymer may be polyethylene glycol and derivatives thereof having an average molecular weight over a range of from about 100 to about 100,000. The compositions may include other components such as fluid, pharmaceutically acceptable carriers to form injectable formulations, and/or biologically active proteins such as growth factors or cytokines.

ABSTRACT WORD COUNT: 134

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

| Available Text | Language | Update | Word Count |
|------------------------------------|-----------|--------|------------|
| CLAIMS A | (English) | EPAB95 | 1084 |
| SPEC A | (English) | EPAB95 | 9832 |
| Total word count - document A | | | 10916 |
| Total word count - document B | | | 0 |
| Total word count - documents A + B | | | 10916 |

6/3,AB/9 (Item 6 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
(c) 2002 European Patent Office. All rts. reserv.

00686988

Clear, chemically-modified collagensynthetic polymer conjugates for ophthalmic applications.

Klare chemisch-modifizierte Kollagenpolymerkonjugate und ihre ophthalmologischen Anwendungen.

Polymères synthétiques et conjugués, claires du collagène chimiquement modifiés et leur application ophtalmologiques.

PATENT ASSIGNEE:

COLLAGEN CORPORATION, (255151), 2500 Faber Place, Palo Alto, California 94303, (US), (applicant designated states:
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LEGAL REPRESENTATIVE:

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PATENT (CC, No, Kind, Date): EP 656214 A1 950607 (Basic)

APPLICATION (CC, No, Date): EP 94117226 941101;

PRIORITY (CC, No, Date): US 147227 931103

DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; NL; SE

INTERNATIONAL PATENT CLASS: A61K-047/48; A61L-027/00; A61L-031/00;

ABSTRACT EP 656214 A1

Various forms of chemically modified collagen are covalently crosslinked with activated synthetic hydrophilic polymers to form optically clear biocompatible conjugates useful in a variety of medical

applications, particularly in ophthalmic devices. The chemically modified collagen is in substantially nonfibrillar form at pH 7 and is preferably succinylated or methylated collagen. The synthetic hydrophilic polymer is preferably an activated polymeric glycol, most preferably, a di-or multifunctionally *activated* *polyethylene* *glycol*. Materials and devices formed with the chemically modified collagen-synthetic polymer conjugates have good optical clarity, mechanical strength, and moldability. (see image in original document)

ABSTRACT WORD COUNT: 94

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

| Available Text | Language | Update | Word Count |
|------------------------------------|-----------|--------|------------|
| CLAIMS A | (English) | EPAB95 | 542 |
| SPEC A | (English) | EPAB95 | 9592 |
| Total word count - document A | | | 10134 |
| Total word count - document B | | | 0 |
| Total word count - documents A + B | | | 10134 |

6/3,AB/10 (Item 7 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
(c) 2002 European Patent Office. All rts. reserv.

00527344

Process for the preparation of siloxane-oxyalkylene copolymers
Verfahren zur Herstellung von Siloxanoxyalkylencopolymeren
Procede de preparation de copolymeres siloxane-oxyalcoylene

PATENT ASSIGNEE:

OSi Specialties, Inc., (1824161), 777 Old Saw Mill River Road Route 100C,
Silicones Building, Tarrytown, NY 10591-6728, (US), (applicant
designated states: AT;BE;CH;DE;ES;FR;GB;IT;LI;NL)

INVENTOR:

McMullen, Anne Kathryn, Rt. 8, Box 331, Marietta, Ohio 45750, (US)
Furbee, Harold Dean, Rt. 1, Box 135, Friendly, West Virginia 26146, (US)
Austin, Paul Edwin, 90 Kittle Street, Williamstown, West Virginia 26187,
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LEGAL REPRESENTATIVE:

von Hellfeld, Axel, Dr. Dipl.-Phys. et al (53042), Wuesthoff & Wuesthoff
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PATENT (CC, No, Kind, Date): EP 535589 A1 930407 (Basic)
EP 535589 B1 970507

APPLICATION (CC, No, Date): EP 92116635 920929;

PRIORITY (CC, No, Date): US 767825 910930

DESIGNATED STATES: AT; BE; CH; DE; ES; FR; GB; IT; LI; NL

INTERNATIONAL PATENT CLASS: C08G-077/46;

ABSTRACT EP 535589 A1

The invention provides an improved solventless hydrosilation process
for preparing a siloxane-oxyalkylene copolymers, the improvement
comprising conducting the reaction in the presence of at least one sodium
metal phosphate.

ABSTRACT WORD COUNT: 31

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

| Available Text | Language | Update | Word Count |
|----------------|-----------|--------|------------|
| CLAIMS A | (English) | EPABF1 | 390 |

PCT/26515

| | | | |
|------------------------------------|-----------|--------|------|
| CLAIMS B | (English) | EPAB97 | 372 |
| CLAIMS B | (German) | EPAB97 | 347 |
| CLAIMS B | (French) | EPAB97 | 381 |
| SPEC A | (English) | EPABF1 | 3298 |
| SPEC B | (English) | EPAB97 | 3417 |
| Total word count - document A | | | 3688 |
| Total word count - document B | | | 4517 |
| Total word count - documents A + B | | | 8205 |

6/3,AB/11 (Item 8 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
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00393651

Process for preparing polyethylene glycol derivatives and modified protein.
Verfahren fur die Herstellung von Polyethylenglykolderivate und
modifizierte Proteine.

Procede pour la preparation de derives de polyethylene glycol et proteine
modifiee.

PATENT ASSIGNEE:

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PATENT (CC, No, Kind, Date): EP 400472 A2 901205 (Basic)

EP 400472 A3 910626

EP 400472 B1 960403

APPLICATION (CC, No, Date): EP 90109806 900523;

PRIORITY (CC, No, Date): JP 89134191 890527; JP 89134192 890527

DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LI; LU; NL; SE

INTERNATIONAL PATENT CLASS: C08G-065/32; C07K-001/00; A61K-047/48;

ABSTRACT EP 400472 A2

High purity polyethylene glycol derivatives of formula (I) are useful
as protein modifiers of interferons, t-PA, EGF, various hormones, etc.

The thus modified protein has minimized antigenicity, prolonged plasma
half life, or improved transfer to tissue. A novel process for preparing
high purity polyethylene glycol derivatives is also disclosed.

ABSTRACT WORD COUNT: 53

LANGUAGE (Publication,Procedural,Application): English; English; English
 FULLTEXT AVAILABILITY:

| Available Text | Language | Update | Word Count |
|------------------------------------|-----------|--------|------------|
| CLAIMS A | (English) | EPABF1 | 534 |
| CLAIMS B | (English) | EPAB96 | 305 |
| CLAIMS B | (German) | EPAB96 | 248 |
| CLAIMS B | (French) | EPAB96 | 335 |
| SPEC A | (English) | EPABF1 | 18791 |
| SPEC B | (English) | EPAB96 | 18765 |
| Total word count - document A | | | 19328 |
| Total word count - document B | | | 19653 |
| Total word count - documents A + B | | | 38981 |

6/3,AB/12 (Item 9 from file: 348)
 DIALOG(R)File 348:EUROPEAN PATENTS
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00382662

CONJUGATION OF POLYMER TO COLONY STIMULATING FACTOR-1.
 KONJUGATION DER POLYMERE AN KOLONIEN STIMULIERENDEN FAKTOR.
 CONJUGAISON D'UN POLYMERE AVEC LA PROTEINE CSF-1.

PATENT ASSIGNEE:

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 AT;BE;CH;DE;FR;GB;IT;LI;LU;NL;SE)

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LEGAL REPRESENTATIVE:

Bizley, Richard Edward et al (28353), HEPWORTH, LAWRENCE BRYER & BIZLEY
 2nd Floor Gate House South West Gate, Harlow Essex CM20 1JN, (GB)

PATENT (CC, No, Kind, Date): EP 402378 A1 901219 (Basic)
 EP 402378 B1 940302
 WO 8906546 890727

APPLICATION (CC, No, Date): EP 89902670 890123; WO 89US270 890123

PRIORITY (CC, No, Date): US 146275 880120

DESIGNATED STATES: AT; BE; CH; DE; FR; GB; IT; LI; LU; NL; SE

INTERNATIONAL PATENT CLASS: A61K-047/00; A61K-037/02;

NOTE:

No A-document published by EPO

LANGUAGE (Publication,Procedural,Application): English; English; English
 FULLTEXT AVAILABILITY:

| Available Text | Language | Update | Word Count |
|------------------------------------|-----------|--------|------------|
| CLAIMS B | (English) | EPBBF1 | 1119 |
| CLAIMS B | (German) | EPBBF1 | 1078 |
| CLAIMS B | (French) | EPBBF1 | 1211 |
| SPEC B | (English) | EPBBF1 | 15788 |
| Total word count - document A | | | 0 |
| Total word count - document B | | | 19196 |
| Total word count - documents A + B | | | 19196 |

6/3,AB/13 (Item 10 from file: 348)
 DIALOG(R)File 348:EUROPEAN PATENTS
 (c) 2002 European Patent Office. All rts. reserv.

00270434

Magnetic material-physiologically active substance conjugate.
 Konjugat von physiologisch aktivem Stoff und magnetischem Material.
 Conjugat de substance physiologiquement active et de materiau magnetique.
 PATENT ASSIGNEE:

Bellex Corporation, (626250), 1-10, Nihonbashi Kayabacho, Chuo-ku Tokyo,
 (JP), (applicant designated states: BE;CH;DE;ES;FR;GB;IT;LI;NL;SE)

INVENTOR:

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 Tokyo, (JP)
 Tamaura, Yutaka, 13-105, 11, Hino 6-chome Konan-ku, Yokohama-shi
 Kanagawa-ken, (JP)
 Takahashi, Katsunobu, 308 Shinkoiwa Sky Mansion 56-10, Shinkoiwa 1-chome,
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LEGAL REPRESENTATIVE:

Ablewhite, Alan James et al , MARKS & CLERK 57/60 Lincoln's Inn Fields,
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PATENT (CC, No, Kind, Date): EP 260098 A2 880316 (Basic)
 EP 260098 A3 880727

APPLICATION (CC, No, Date): EP 87307898 870907;

PRIORITY (CC, No, Date): JP 86209982 860906; JP 86252479 861023

DESIGNATED STATES: BE; CH; DE; ES; FR; GB; IT; LI; NL; SE

INTERNATIONAL PATENT CLASS: C07K-017/08; C12N-011/08;

ABSTRACT EP 260098 A2

Disclosed is a conjugate comprising a magnetic material and a
 physiologically active substance bound to each other through a
 polyethylene glycol derivative, and a conjugate comprising a magnetic
 material and a polyethylene glycol derivative bound to each other.

According to the present invention, a bioreactor enabling application
 to or recovery of physiologically active substances under liquid state by
 utilizing the magnetic properties is provided.

ABSTRACT WORD COUNT: 68

LANGUAGE (Publication,Procedural,Application): English; English; English

FULLTEXT AVAILABILITY:

| Available Text | Language | Update | Word Count |
|------------------------------------|-----------|--------|------------|
| CLAIMS A | (English) | EPABF1 | 359 |
| SPEC A | (English) | EPABF1 | 9766 |
| Total word count - document A | | | 10125 |
| Total word count - document B | | | 0 |
| Total word count - documents A + B | | | 10125 |

| Set | Items | Description |
|-----|-------|----------------------------------|
| S7 | 51 | AU=(TALARICO, T? OR TALARICO T?) |
| S8 | 82 | AU=(STACEY, C? OR STACEY C?) |
| S9 | 5 | S7 AND S8 |
| S10 | 2 | (S7 OR S8) AND (S1 OR S3 OR S4) |
| S11 | 3 | (S9 OR S10) NOT S5 |
| S12 | 1 | RD (unique items) |

>>>No matching display code(s) found in file(s): 65, 113

- Author(s)

12/3,AB/1 (Item 1 from file: 440)
 DIALOG(R)File 440:Current Contents Search(R)
 (c) 2002 Inst for Sci Info. All rts. reserv.

11225349 References: 50

TITLE: Chemical characterization of pyridoxalated hemoglobin
 polyoxyethylene conjugate

AUTHOR(S): *Talarico TL (REPRINT)*; Guise KJ; *Stacey CJ*

AUTHOR(S) E-MAIL: talarico@mindspring.com

CORPORATE SOURCE: Apex Biosci Inc, POB 12847/Res Triangle Pk//NC/27709

(REPRINT); Apex Biosci Inc, /Res Triangle Pk//NC/27709

PUBLICATION TYPE: JOURNAL

PUBLICATION: BIOCHIMICA ET BIOPHYSICA ACTA-PROTEIN STRUCTURE AND MOLECULAR
 ENZYMOLOGY, 2000, V1476, N1 (JAN 3), P53-65

GENUINE ARTICLE#: 271FD

PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS

ISSN: 0167-4838

LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Pyridoxalated hemoglobin polyoxyethylene conjugate (PHP) was developed in the 1980s as an oxygen carrier and is now under development for treatment of nitric oxide-dependent, volume refractory shock. PHP is made by derivatizing human stroma-free hemoglobin with pyridoxal-5-phosphate and polyoxyethylene (POE). A unique aspect of using POE for modification is that unlike its mono-methoxy polyethylene glycol (PEC) relatives, POE is bifunctional. The result of derivatization of stroma-free hemoglobin is a complex mixture of modified hemoglobin and other red cell proteins. The molecular weight profile, based on size exclusion chromatography, is bimodal and has a number average molecular weight of approximately 105 000 and a weight average molecular weight of approximately 187 000. The mixture of hemoglobin molecules has on average 3.3 pyridoxal and 5.0 polyoxyethylene units per tetramer. A portion of the tetramers are linked by POE crosslinks. The hemoglobin tetramers retain their ability to dissociate into dimer pairs and only a small percentage of the dimer pairs are not modified with POE. The SDS-PAGE profile exhibits the ladder-like appearance commonly associated with polyethylene glycol-modified proteins. The isoelectric focusing profile is broad, demonstrating a pr range of 5.0-6.5. The hydrodynamic size of PHP was determined to be approximately 7.2 nm by dynamic light scattering. Soluble red blood cell proteins, such as catalase, superoxide dismutase, and carbonic anhydrase, are present in PHP and are also modified by POE. (C) 2000 Elsevier Science B.V. All rights reserved.

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PCT/26515

TITLE: Oxygen carrier for blood substitutes
INVENTOR(S): Iwashita, Yuji; Iwasaki, Keiji; Ajisaka, Katsumi
PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan
SOURCE: Eur. Pat. Appl., 15 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| EP 67029 | A2 | 19821215 | EP 1982-302826 | 19820602 |
| EP 67029 | A3 | 19830803 | | |
| EP 67029 | B1 | 19860430 | | |
| R: DE, FR, GB | | | | |
| JP 57206622 | A2 | 19821218 | JP 1981-89315 | 19810610 |
| JP 02006337 | B4 | 19900208 | | |
| US 4412989 | A | 19831101 | US 1982-384606 | 19820603 |

PRIORITY APPLN. INFO.: JP 1981-89315 19810610

AB An O carrier is prepd. by introducing at least 1 CO₂H group into a polyalkylene glycol or polyether and covalently bonding the polymer to an NH₂ group of a **Hb** or a **Hb** deriv. by amidation. Thus, monomethoxy polyethylene glycol succinate [79934-70-6] was stirred overnight at room temp. with N-hydroxysuccinimide in DMF in the presence of dicyclohexylcarbodiimide, the dicyclohexylurea ppt. was sepd. by **filtration**, and Et₂O was added to the **filtrate** to obtain monomethoxy polyethylene glycol mono(succinimidyl succinate) [78274-32-5], which was **filtered** and added at 0.degree. to a pH 8.5 soln. of the pyridoxal 5-phosphate deriv. of **Hb**. The product was purified by ultrafiltration, and freeze-dried to give a modified **Hb** with a degree of substitution of 6.0 and a mol. wt. of 95,000. The half-lives of the **Hb**-polyether complexes in the circulatory system of rats were 4-7-fold those of **Hb**, and the complexes showed good ability to deliver O to the tissues.

IT 25322-68-3

RL: RCT (Reactant)
(esterification of, with succinic anhydride)

L20 ANSWER 33 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1982:62768 HCAPLUS

DOCUMENT NUMBER: 96:62768

TITLE: Renal toxicity of **hemoglobin** derivatives as blood substitute

AUTHOR(S): Iwashita, Yuji; Ajisaka, Katsumi

CORPORATE SOURCE: Cent. Res. Lab., Ajinomoto Co., Inc., Kawasaki, Japan

SOURCE: Organ-Directed Toxic.: Chem. Indices Mech., Proc. Symp. (1981), 97-101. Editor(s): Brown, Stanley S.; Davies, Donald Selwyn. Pergamon: Oxford, Engl.
CODEN: 46XDAG

DOCUMENT TYPE: Conference

LANGUAGE: English

AB The relation between the clearance rate of infused **Hb** derivs. in the circulation of rats and their physicochem. properties

Searcher : Shears 308-4994

was studied. When the mol. wt. of the Hb derivs. was .apprx.20,000, half of the infused deriv. disappeared in .apprx.30 min. When the mol. wt. was .apprx.40,000, the half-disappearance time was .apprx.50 min. In these cases, gross hemoglobinuria appeared. Infusion of a series of polyethylene glycol-substituted Hbs revealed a close correlation between the retention vol. on gel chromatog. and the half-disappearance time. Apparently, the glomerular filtration of the Hb derivs. is analogous to the permeation through polysaccharide gel.

IT 25322-68-3D, Hb derivs.

RL: BIOL (Biological study)

(kidney clearance and physicochem. properties of, as blood substitutes, kidney toxicity in relation to)

L20 ANSWER 34 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1981:420810 HCAPLUS

DOCUMENT NUMBER: 95:20810

TITLE: Water and protein permeation through polymeric membrane having mechanochemically expanding and contracting pores. Function of chemical valve. I

AUTHOR(S): Osada, Yoshihito; Takeuchi, Yohsuke

CORPORATE SOURCE: Dep. Chem., Ibaraki Univ., Mito, 310, Japan

SOURCE: J. Polym. Sci., Polym. Lett. Ed. (1981), 19(6), 303-8

CODEN: JPYBAN; ISSN: 0360-6384

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Increased H2O permeation and protein flow rates were obsd. in poly(methacrylic acid) membranes with PEG. H2O permeability was dependent on PEG mol. wt. The performance of protein sepn. by the membranes was improved 240 fold for albumin and 55 fold for Hb with PEG treatment. The membranes are suggested for ultrafiltration.

IT 25322-68-3

RL: ANST (Analytical study)

(protein and water permeation through polymethacrylate membranes response to)

L20 ANSWER 35 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1979:571234 HCAPLUS

DOCUMENT NUMBER: 91:171234

TITLE: Artificial feces for use as controls in analysis of fecal matter

PATENT ASSIGNEE(S): Roehm G.m.b.H., Fed. Rep. Ger.

SOURCE: Fr. Demande, 18 pp.

CODEN: FRXXBL

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|----------|-----------------|----------|
| FR 2393309 | A1 | 19781229 | FR 1978-16092 | 19780530 |
| FR 2393309 | B1 | 19821231 | | |
| DE 2724438 | C2 | 19790510 | DE 1977-2724438 | 19770531 |
| DE 2819284 | A1 | 19791115 | DE 1978-2819284 | 19780502 |

PCT/26515

| | | | | |
|------------------------|----|----------|-----------------|----------|
| DE 2819284 | C2 | 19851219 | | |
| AT 7803515 | A | 19800615 | AT 1978-3515 | 19780516 |
| AT 360660 | B | 19810126 | | |
| GB 1579102 | A | 19801112 | GB 1978-21978 | 19780524 |
| SE 7806291 | A | 19781201 | SE 1978-6291 | 19780530 |
| SE 443239 | B | 19860217 | | |
| SE 443239 | C | 19860529 | | |
| US 4394452 | A | 19830719 | US 1978-910285 | 19780530 |
| JP 54017794 | A2 | 19790209 | JP 1978-65593 | 19780531 |
| JP 62036180 | B4 | 19870805 | | |
| CA 1119922 | A1 | 19820316 | CA 1978-304546 | 19780531 |
| CH 636965 | A | 19830630 | CH 1978-5960 | 19780531 |
| PRIORITY APPLN. INFO.: | | | DE 1977-2724438 | 19770531 |
| | | | DE 1978-2819284 | 19780502 |

AB Artificial feces for use as std. controls in the detection of occult blood in fecal samples via detection of **Hb** peroxidase by a color reaction is described. The std. consists of a polymeric matrix contg. an acid, a coloring material that produces a coloration similar to feces, water and(or) lubricants, drying agents, and preservatives. For example, 5.5 g Tylose MH 20 was placed in suspension in 8.9 g EtOH, 540 g H2O was added, and the mixt. was stirred for 15 min. Sephadex G 25 (10 g) was added, followed by Na benzoate (14.5 g) and glycerol (73.1 g). The mixt. was shaken for 3 h. Avicel 333, brown Fe oxide 9.0, and yellow Fe oxide 6.0 g were mixed to the dry state and added to the previous mixt. and then kneaded. Blood is then added at .apprx.1.5% by wt. to the mixt., giving a std. with a blood content in the range of normal fecal samples.

IT **25322-68-3 32131-17-2**, biological studies
 RL: BIOL (Biological study)
 (in feces std.)

L20 ANSWER 36 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1979:182779 HCAPLUS

DOCUMENT NUMBER: 90:182779

TITLE: Apparatus for production of control solutions

INVENTOR(S): Rapkin, Myron C.

PATENT ASSIGNEE(S): Miles Laboratories, Inc., USA

SOURCE: Ger. Offen., 22 pp.
 CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|----------|
| ----- | ---- | ----- | ----- | ----- |
| DE 2835296 | A1 | 19790301 | DE 1978-2835296 | 19780811 |
| FR 2400708 | A1 | 19790316 | FR 1978-23246 | 19780807 |
| GB 2002516 | A | 19790221 | GB 1978-33097 | 19780811 |
| SE 7808620 | A | 19790216 | SE 1978-8620 | 19780814 |
| JP 54032382 | A2 | 19790309 | JP 1978-98282 | 19780814 |
| BR 7805219 | A | 19790424 | BR 1978-5219 | 19780814 |
| PRIORITY APPLN. INFO.: | | | US 1977-824399 | 19770815 |

AB The components of std. solns. are impregnated into **filter** paper strips and lyophilized, and the dried strips are added to appropriate solvents to form the std. solns. for anal. Thus, a 8.9 .times. 53.3 cm strip of **filter** paper was soaked in 50 mL

of a soln. contg. 25 g glucose/dL and 0.5 g Yellow 5 and then dried and cut into 0.5 .times. 0.5-cm pieces. A soln. simulating diabetic urine was produced by soaking a piece in water for 20 min with intermittent stirring. Std. soln. preps. also are described for the detection of nitrite, proteins, blood, urobilinogens, ketone bodies, and bilirubin in urine, for the detn. of Cl and alky. in swimming pool water, for the detn. of corrosion inhibitors and capacity of antifreezes, and for the detn. of acidity in fruit juices.

IT 25322-68-3

RL: ANST (Analytical study)
(std. soln. contg., filter paper carrier for, for
antifreeze capacity detn.)

L20 ANSWER 37 OF 37 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1965:476534 HCAPLUS
DOCUMENT NUMBER: 63:76534
ORIGINAL REFERENCE NO.: 63:14096g-h
TITLE: Behavior of polyethylene glycol on dialysis and
gel filtration
AUTHOR(S): Ryle, A. P.
CORPORATE SOURCE: Univ. Edinburgh, UK
SOURCE: Nature (1965), 206(4990), 1256
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Polyethylene glycol (I) was dialyzed against 100 ml. of distd. H2O in a sack of 24/32 in. "Visking" tubing until the sack was apparently empty. The contents of the sack was rinsed with distd. H2O and a residue of 27 mg. was obtained by freeze-drying. Elution curves from gel filtration of unfractionated I, residue from the dialysis, hemoglobin and pepsin C indicate that gel filtration is not a suitable means of sepg. I from proteins of moderate mol. wt. Columns of diethylaminoethyl or carboxymethyl cellulose did not retard the flow of I.

IT 25322-68-3, Glycols, polyethylene
(dialysis and gel filtration of)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, PHIC,
PHIN, TOXCENTER' ENTERED AT 10:53:46 ON 17 OCT 2002)

19 S L20

12 DUP REM 121 (7-DUPLICATES REMOVED)

L22 ANSWER 1 OF 12 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001070158 EMBASE
TITLE: Purification and characterization of superoxide
dismutase from chicken liver.
AUTHOR: Ozturk-Urek R.; Tarhan L.
CORPORATE SOURCE: L. Tarhan, Department of Chemistry, Faculty of Art
and Science, University of Dokuz Eylul, 35150 Buca,
Izmir, Turkey. leman.tarhan@deu.edu.tr
SOURCE: Comparative Biochemistry and Physiology - B
Biochemistry and Molecular Biology, (2001) 128/2
(205-212).
Refs: 28
ISSN: 1096-4959 CODEN: CBPBB8
PUBLISHER IDENT.: S 1096-4959(00)00300-6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB Superoxide dismutase (SOD; EC 1.15.1.1) is an enzyme that protects against oxidative stress from superoxide radicals in living cells. This enzyme has been isolated, purified and partially characterized from chicken liver. The following steps were carried out in order to purify chicken liver SOD. Initially, the liver was homogenized and **hemoglobin** was removed. Subsequently protein precipitation was effected with (NH₄)₂SO₄, methanol, (NH₄)₂SO₄-methanol and polyethylene glycol methods. The product from polyethylene glycol-3350 precipitation was found to have the highest SOD activity. Polyethylene glycol was removed by chromatography using a PD-10 column. After passing through an ultrafilter, the superoxide dismutase was fractionated by DEAE-ion chromatography and then Sephadex G-75 gel **filtration** chromatography. During this purification procedure, a specific activity of 4818.2 IU/mg was reached, corresponding to 285.8-fold purification. The purified enzyme, which was characterized as cyanide-sensitive SOD, contained two subunits having Cu and Zn elements with a molecular weight of 16000 +/- 500 for each. The optimum pH of purified CuZnSOD was determined to be 8.9. The enzyme was found to have good pH stability in the pH range 6.0-7.5 at 25.degree.C over a 2-h incubation period and displayed good thermal stability up to 45.degree.C at pH 7.4 over a 1-h incubation period. The SOD enzyme was not inhibited by DTT and .beta.-mercaptoethanol, but inhibited by CN(-) and H₂O₂. In the presence of 2 mM iodoacetamide, the enzyme showed an approximately 40% activity loss. Finally, the inhibitory effect of ionic strength on SOD was also investigated. .COPYRG. 2001 Elsevier Science Inc.

L22 ANSWER 2 OF 12 WPIDS (C) 2002 THOMSON DERWENT

ACCESSION NUMBER: 2000-317863 [27] WPIDS

DOC. NO. NON-CPI: N2000-238553

DOC. NO. CPI: C2000-096229

TITLE: Production of a **hemoglobin** solution from a solution containing red blood cells using a centrifuge, useful as an inexpensive blood substitute during transfusions.

DERWENT CLASS: A96 B04 D16 P34

INVENTOR(S): VANDEGRIFF, K D; WINSLOW, R M

PATENT ASSIGNEE(S): (SANG-N) SANGART INC

COUNTRY COUNT: 91

PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|------|----------|-----------|----|----|
| WO 2000021591 | A1 | 20000420 | (200027)* | EN | 23 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC | | | | | |
| MW NL OA PT SD SE SL SZ TZ UG ZW | | | | | |
| W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM | | | | | |
| EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ | | | | | |
| LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU | | | | | |
| SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW | | | | | |
| AU 2000011170 | A | 20000501 | (200036) | | |
| EP 1121165 | A1 | 20010808 | (200146) | EN | |
| R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE | | | | | |
| BR 9915734 | A | 20011002 | (200167) | | |

KR 2001099700 A 20011109 (200229)
CN 1332646 A 20020123 (200231)

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---------------|------|-----------------|----------|
| WO 2000021591 | A1 | WO 1999-US24149 | 19991015 |
| AU 2000011170 | A | AU 2000-11170 | 19991015 |
| EP 1121165 | A1 | EP 1999-954950 | 19991015 |
| | | WO 1999-US24149 | 19991015 |
| BR 9915734 | A | BR 1999-15734 | 19991015 |
| | | WO 1999-US24149 | 19991015 |
| KR 2001099700 | A | KR 2001-704781 | 20010416 |
| CN 1332646 | A | CN 1999-813429 | 19991015 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---------------|-------------|--------------|
| AU 2000011170 | A Based on | WO 200021591 |
| EP 1121165 | A1 Based on | WO 200021591 |
| BR 9915734 | A Based on | WO 200021591 |

PRIORITY APPLN. INFO: US 1999-122180P 19990301; US 1998-104319P
19981015

AN 2000-317863 [27] WPIDS

AB WO 200021591 A UPAB: 20000606

NOVELTY - A method (M1) for producing **hemoglobin** solution from a solution containing red blood cells (RBCs) using a centrifuge, is new.

DETAILED DESCRIPTION - A method (M1) for producing **hemoglobin** solution from a solution containing RBCs using a centrifuge comprises:

(a) isolating the RBCs in the solution;
(b) removing the supernatant produced during the step of isolating followed by washing the RBCs;

(c) lyzing the RBCs to produce a hemolysate; and

(d) separating stromata of the RBCs from the hemolysate.

INDEPENDENT CLAIMS are also included for the following:

(1) a method (M2) for producing **hemoglobin** from a solution containing RBCs and plasma comprising:

(a) collecting the solution in a sterile processing set comprising a processing bag and a tube harness, where the processing bag is disposed within a centrifuge in the cell processing apparatus;

(b) separating the RBCs from the plasma by rotating the processing bag within the centrifuge;

(c) expressing the plasma from the processing bag;

(d) introducing a washing solution into the processing bag;

(e) lyzing the RBCs by introducing distilled water into the processing bag to liberate **hemoglobin**;

(f) separating RBC membranes from the **hemoglobin** solution by rotating the processing bag in the centrifuge; and

(g) removing the **hemoglobin** solution through a sterile port in the processing bag; and

(2) a method (M3) for preparing a modified **hemoglobin** solution comprising isolating the **hemoglobin** solution as

in M1 and reacting with reagents adapted for chemical modification of the solution.

USE - The method is useful for producing high-quality **hemoglobin** solution which can be used as a blood substitute for transfusions.

ADVANTAGE - The method allows the preparation of high-quality blood substitutes with reduced cost, complexity and risk of contamination.

Dwg.0/4

L22 ANSWER 3 OF 12 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 1

ACCESSION NUMBER: 1997:408801 BIOSIS

DOCUMENT NUMBER: PREV199799715004

TITLE: The impact of polyethylene glycol conjugation on bovine **hemoglobin**'s circulatory half-life and renal effects in a rabbit top-loaded transfusion model.

AUTHOR(S): Conover, Charles D. (1); Gilbert, Carl W.; Shum, Kwok L.; Shorr, Robert G. L.

CORPORATE SOURCE: (1) Res. Dev. Formulations-Toxicol. Dep., Enzon Inc., 20 Kingsbridge Rd., Piscataway, NJ 08854 USA

SOURCE: Artificial Organs, (1997) Vol. 21, No. 8, pp. 907-915.
ISSN: 0160-564X.

DOCUMENT TYPE: Article

LANGUAGE: English

AB This study compares the effects of polyethylene glycol (PEG) modified bovine **hemoglobin** on vascular half-life and renal function in rabbits to those of unmodified bovine **hemoglobin**. Renal function was assessed by the measurement of the glomerular **filtration** rate, urinalysis, blood chemistries, **hemoglobin** (Hb) excretion rates, and tissue histology. The influence of infusion rates on **hemoglobin** excretion rates and organ morphology was also examined. The mean half-life of unmodified bovine **hemoglobin** was 3.0 \pm 0.1 (mean \pm SEM) h, which was extended 14-fold to 43.2 \pm 1.7 h following PEG conjugation. The glomerular **filtration** rate, urinalysis, and blood chemistries were not greatly affected by either the unmodified bovine **hemoglobin** or the PEG modified bovine **hemoglobin**. However, unmodified bovine **hemoglobin** did demonstrate significant hemoglobinuria (Hb excretion levels in excess of 1.0% of the infused dose (p \leq 0.05)) at all infusion rates given while PEG modified bovine **hemoglobin** did not. In addition, histological examination by light microscopy indicated that the most severe morphological changes occurred in animals that received unmodified bovine **hemoglobin**. This data suggests that PEG modification of bovine **hemoglobin** significantly reduced some of the adverse effects of bovine **hemoglobin** on renal physiology and morphology.

L22 ANSWER 4 OF 12 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 97310947 MEDLINE

DOCUMENT NUMBER: 97310947 PubMed ID: 9167846

TITLE: Detection of residual polyethylene glycol derivatives in pyridoxylated-**hemoglobin**-polyoxyethylene conjugate.

AUTHOR: Miles P J; Langley K V; Stacey C J; Talarico T L
 CORPORATE SOURCE: Apex Bioscience, Inc., Research Triangle Park, NC 27709, USA.
 SOURCE: ARTIFICIAL CELLS, BLOOD SUBSTITUTES, AND IMMOBILIZATION BIOTECHNOLOGY, (1997 May) 25 (3) 315-26.
 Journal code: 9431307. ISSN: 1073-1199.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199707
 ENTRY DATE: Entered STN: 19970805
 Last Updated on STN: 19970805
 Entered Medline: 19970721

AB Purified **hemoglobin** solutions have been shown to cause renal toxicity in animals. Safe use of **hemoglobin** based therapeutics in humans requires modification of the **hemoglobin** molecule to prevent this toxicity. **Hemoglobin** modification may be accomplished by crosslinking the dimers within the **hemoglobin** tetramer or by derivatization of the alpha and/or beta subunits such that their size and/or charge prevents **filtration** by the glomeruli. Pyridoxylated **hemoglobin polyoxyethylene** conjugate (PHP) consists of **hemoglobin** molecules modified with **alpha-carboxymethyl**, omega-carboxymethoxy **polyoxyethylene** (POE). We have developed a high performance liquid chromatography-based (HPLC) method which can quantitate residual **POE** at levels of 0.1 mg/ml or greater. The detection of **POE** at this level of sensitivity requires the use of an evaporative light scattering detector (ELSD). A differential refractometer may also be used for **POE** detection, however the limit of quantitation for this detector is approximately 10 fold greater than that observed for the evaporative light scattering detector, resulting in a reduction in sensitivity. The successful use of this method requires sample deproteination using trichloroacetic acid. The reliability of the method has been demonstrated by spike recovery, precision, and reproducibility studies in PHP and buffer solutions.

L22 ANSWER 5 OF 12 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1997:106004 BIOSIS

DOCUMENT NUMBER: PREV199799405207

TITLE: Surface modification of **hemoglobin** vesicles with poly(ethylene glycol) and effects on aggregation, viscosity, and blood flow during 90 percent exchange transfusion in anesthetized rats.

AUTHOR(S): Sakai, Hiromi; Takeoka, Shinji; Park, Sung Ick; Kose, Takehiro; Nishide, Hiroyuki; Izumi, Yotaro; Yoshizu, Akira; Kobayashi, Koichi; Tsuchida, Eishun (1)

CORPORATE SOURCE: (1) Dep. Polymer Chem., Advanced Res. Inst. Sci. Eng., Waseda Univ., Tokyo 169 Japan

SOURCE: Bioconjugate Chemistry, (1997) Vol. 8, No. 1, pp. 23-30.

ISSN: 1043-1802.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Poly(ethylene glycol) (PEG-5000)-conjugated phosphatidylethanolamine

was introduced onto the surface of **hemoglobin** vesicles (HbV); phospholipid vesicles encapsulating concentrated Hb ($d = 0.257 \pm 0.087 \mu\text{-m}$; P-50 = 32 Torr). The obtained PEG-modified HbV (HbV-PEG) was studied for use as a red cell substitute from the viewpoint of rheology, surface properties, and hemodynamics. The viscosity of the unmodified HbV suspended in saline ((Hb) = 10 g/dL) was 2.6 cP (shear rate = 358 s⁻¹, 37 degree C), less than that of human blood (4 cP). However, when suspended in a 5 g/dL albumin solution (HbV/albumin), it increased to 8 cP due to the molecular interaction between albumin and vesicles, and the viscosity increased with decreasing shear rate, e.g., 37 cP at 0.58 s⁻¹. As for the HbV-PEG/albumin, on the other hand, the viscosity was 3.5 cP at 358 s⁻¹ and was comparable with that of human blood. Optical microscopy showed formless flocculated aggregates of the unmodified HbV, while no aggregates were confirmed for the HbV-PEG. The steric hindrance of PEG chains seemed to be effective in capillaries, the suspensions were allowed to penetrate through isopore membrane **filters** (pore size = 0.4-8 $\mu\text{-m}$, cf. capillary diameter = 4-10 $\mu\text{-m}$). The penetration rate of the HbV-PEG/albumin was higher than that of the unmodified HbV/albumin due to the suppression of aggregation, whereas both of them were significantly higher than that of human blood due to the smaller size of vesicles than RBC. Ninety percent exchange transfusion was performed with the HbV-PEG/albumin or HbV/albumin in anesthetized Wistar rats ($n = 6$). The blood flow in the abdominal aorta increased 1.5 times, and the total peripheral resistance decreased in the HbV-PEG/albumin-administered group in comparison with the HbV/albumin group. As for the blood gas parameters, the base excess and pH remained at higher levels in the HbV-PEG/albumin group, and the O₂ tension in mixed venous blood for the HbV-PEG/albumin group tended to be maintained at a higher level than that for the HbV/albumin group. Thus, the PEG modification of HbV reduced the viscosity by the suppression of aggregation and resulted in prompt blood circulation in vivo.

L22 ANSWER 6 OF 12 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
 ACCESSION NUMBER: 1995:288270 BIOSIS
 DOCUMENT NUMBER: PREV199598302570
 TITLE: PEG-**hemoglobin**: Effect on renal function in various laboratory animal models.
 AUTHOR(S): Conover, C. D.; Sedlatschek, L.; Shum, K.; Shorr, R.
 CORPORATE SOURCE: Enzon Inc., Piscataway, NJ USA
 SOURCE: Journal of Investigative Medicine, (1995) Vol. 43, No. SUPPL. 2, pp. 352A.
 Meeting Info.: Clinical Research Meeting San Diego, California, USA May 5-8, 1995
 DOCUMENT TYPE: Conference
 LANGUAGE: English

L22 ANSWER 7 OF 12 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 94263225 EMBASE
 DOCUMENT NUMBER: 1994263225
 TITLE: Characteristics of Neo Red Cells, their function and safety: In vivo studies.
 AUTHOR: Ogata Y.; Goto H.; Sakaguchi K.; Suzuki M.; Obsaki K.; Suzuki K.; Saniabadi A.P.; Kamitani T.; Takahashi A.
 CORPORATE SOURCE: R and D Center TERUMO Corp, 1500 Inokuchi, Nakai-

SOURCE: machi, Kanagawa 259-01, Japan
 Artificial Cells, Blood Substitutes, and
 Immobilization Biotechnology, (1994) 22/3 (875-881).
 ISSN: 1073-1199 CODEN: ABSBE4

COUNTRY: United States

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 025 Hematology
 027 Biophysics, Bioengineering and Medical
 Instrumentation

LANGUAGE: English

SUMMARY LANGUAGE: English

AB A new type of artificial oxygen carriers, the Neo Red Cells (NRCs) have been developed and investigated for oxygen transporting efficiency and safety in experimental animals. Stroma free **hemoglobin** from outdated human red blood cells together with inositol hexaphosphate as an allosteric effector under sterile, pyrogen free condition were encapsulated in liposomes and then were coated with polyethylene glycol bond to hydrogenated soy phosphatidylethanolamine as a surface modifier to prevent aggregation of NRCs in plasma. The efficiency of the NRCs in tissue oxygenation was studied in rabbits which were made severely anemic by drawing 85% of their blood and immediately replacing it with NRC solution. The animals, all recovered to pre-anemic conditions within 6-8 hr and lived normally until being sacrificed, 6 months after the exchange transfusion. The circulation half-life and tissue distribution of NRCs were studied using radiolabeled NRCs. Within the circulation, the halflife of NRCs was 21 hr and extravascularly, they were distributed mainly in and metabolized by the reticuloendothelial system within 7 days. Our observations suggest that the NRCs prepared and investigated in this study are efficient oxygen carriers without causing serious adverse reactions and can be prepared free from pathogenic micro-organisms by special **filtration** technique before encapsulation of **Hb**. Currently, experiments are ongoing to control auto-oxidation of oxyHb to metHb which is higher in NRCs than in native red cells at physiological conditions.

L22 ANSWER 8 OF 12 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
 DUPLICATE 3

ACCESSION NUMBER: 1994:431494 BIOSIS

DOCUMENT NUMBER: PREV199497444494

TITLE: Hemoglobinuria in rats: A sensitive test of renal **filtering** and absorption of PEG-**hemoglobin**, a red blood cell substitute.

AUTHOR(S): Gilbert, C.; Nho, K.; Johnson, M.; Linberg, R.; Shorr, R.

CORPORATE SOURCE: Enzon, Inc., Piscataway, NJ 08854 USA

SOURCE: Artificial Cells Blood Substitutes and Immobilization Biotechnology, (1994) Vol. 22, No. 3, pp. 535-541.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Hemoglobinuria, defined as **hemoglobin** or **hemoglobin** subunits in the urine, is an easily monitored, sensitive indicator of renal handling of **hemoglobin**-based blood substitutes. **Hemoglobin** tetramer dissociation increases **filtration** by the kidneys. When the rate of **filtration** exceeds reabsorption, hemoglobinuria occurs. This study investigates the renal **filtration** and absorption of

polyethylene glycol-modified bovine **hemoglobin** by
monitoring for hemoglobinuria in several model systems.

L22 ANSWER 9 OF 12 TOXCENTER COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1993:151155 TOXCENTER
 COPYRIGHT: Copyright 2002 ACS
 DOCUMENT NUMBER: CA11903020160F
 TITLE: Renal effects of multiple infusion of pyridoxalated-
hemoglobin-polyoxyethylene conjugate (PHP)
 solution in dogs
 AUTHOR(S): Takahashi, Tsuyoshi; Iwasaki, Keiji; Malchesky, Paul
 S.; Harasaki, Hiroaki; Matsushita, Michiaki; Nose,
 Yukihiro; Rolin, Henry, III; Hall, Philip M.
 CORPORATE SOURCE: Dep. Artif. Organs, Cleveland Clin. Found.,
 Cleveland, OH, USA.
 SOURCE: Artificial Organs, (1993) Vol. 17, No. 3, pp.
 153-63.
 CODEN: ARORD7. ISSN: 0160-564X.
 COUNTRY: UNITED STATES
 DOCUMENT TYPE: Journal
 FILE SEGMENT: CAPLUS
 OTHER SOURCE: CAPLUS 1993:420160
 LANGUAGE: English
 ENTRY DATE: Entered STN: 20011116
 Last Updated on STN: 20020917

AB Pyridoxalated-**Hb**-polyoxyethylene conjugate (PHP), which is
 made from out-dated human red blood cells by two major chem.
 modifications, namely pyridoxalation and conjugation with
 polyoxyethylene (POE), is currently under development as a physiol.
 oxygen carrier. This study assessed the effects of PHP-88 soln.,
 which contains 8% (wt/vol) each of **Hb** and maltose, on
 renal function when it was infused 3 times every other day into the
 intact circulation of 8 dogs (5 dogs for the PHP group and 3 for the
 control group; 20 mL/kg for the first infusion, and 10 mL/kg each
 for the second and third infusions, at the rate of 2.5 mL/h/kg).
 Serial detns. of glomerular **filtration** rate (GFR) and
 renal plasma flow (RPF) were carried out pre- and postinfusion for
 up to 3 mo along with measurements of blood and urine analyses,
 urine output rate, fractional excretion of sodium (FES), and free
 water clearance (CH2O). The results showed that plasma colloid
 osmotic pressure (COP) elevated at an av. of 3.3 mm Hg ($p = 0.0085$),
 and GFR and RPF tended to increase by 13% (NS) and 38% (NS), resp.,
 immediately after the third infusion with PHP soln. Urine output
 rate increased during and after the infusion, and FES and CH2O also
 increased for 24 h after the infusion in both groups. Blood urea
 nitrogen, serum creatinine, and serum Na⁺ concns. were not affected
 greatly by the infusions, but hematocrit was decreased by 8% in the
 PHP group, indicating approx. a 42% expansion of plasma vol. These
 changes were obsd. to return to their preinfusion levels by 1 wk
 postinfusion. Renal histol. of the PHP group obtained at 2 wk
 postinfusion revealed vacuole formation in the proximal tubules
 which was not assocd. with any pathol. changes indicative of cell
 death or regeneration. In 4 out of 5 dogs at 3 mo postinfusion
 (necropsy), the vacuoles were not present. Though urinary N-acetyl
 .beta.-glucosaminidase (NAG) activity had significantly increased
 after infusion, it returned to the preinfusion level by 1 mo
 postinfusion. No detrimental effect of vacuoles on the assessed
 renal tubular functions was confirmed in the present study. The

results demonstrated that multiple infusions of PHP solns. were well tolerated in normal dogs, and the obsd. effects were conceived predominantly attributable to the physiol. response of the kidneys to an oncotic load into the circulation, which produced plasma vol. expansion.

L22 ANSWER 10 OF 12 TOXCENTER COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1991:118489 TOXCENTER
 COPYRIGHT: Copyright 2002 ACS
 DOCUMENT NUMBER: CA11408069107E
 TITLE: Preparation and use of polymer-coated affinity supports for hemoperfusion
 AUTHOR(S): Mazid, Abdul M.
 CORPORATE SOURCE: ASSIGNEE: ChembioMed Ltd.
 PATENT INFORMATION: EP 371636 A2 6 Jun 1990
 SOURCE: (1990) Eur. Pat. Appl., 26 pp.
 CODEN: EPXXDW.
 COUNTRY: CANADA
 DOCUMENT TYPE: Patent
 FILE SEGMENT: CAPLUS
 OTHER SOURCE: CAPLUS 1991:69107
 LANGUAGE: English
 ENTRY DATE: Entered STN: 20011116
 Last Updated on STN: 20021015

AB A method is provided for coating chromatog. particulate supports to give a biocompatible outer layer of synthetic membrane-type film which prevents the release of fines but permits adsorption of components to an affinity ligand. The membrane-type coating has a pore size of .gtoreq.20 .ANG.. The coating process is described. Thus, PEG-300 (pore-controlling component) was added to polystyrene in trichloroethylene, followed by addn. of a haptenized support comprising the 8-azidocarbonyloctyl deriv. of trisaccharide A conjugated to diatomite. Following evapn. of solvent, the matrix was wetted, washed, and dried. The polystyrene-coated matrix was relatively free of fines, as compared to controls. When different amts. of PEG-300 were added, 1% PEG-300 gave results superior to those in which higher (4 and 28%) amts. were used. There was little, if any, nonspecific adsorption of essential blood components (platelets, white and red blood cells, **Hb**) to the matrix. In a simulated hemoperfusion, very little or no changes in concn. were found for total protein, albumin, bilirubin, cholesterol, alk. phosphatase, or lactic dehydrogenase; antibody to A1 antigen was adsorbed by the affinity ligand.

L22 ANSWER 11 OF 12 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
 ACCESSION NUMBER: 1984:352482 BIOSIS
 DOCUMENT NUMBER: BA78:88962
 TITLE: CALMODULIN BINDING PROTEINS VISUALIZATION BY IODINE-125 LABELED CALMODULIN OVERLAY ON BLOTS QUENCHED WITH TWEEN 20 OR BOVINE SERUM ALBUMIN AND POLY ETHYLENE OXIDE.
 AUTHOR(S): FLANAGAN S D; YOST B
 CORPORATE SOURCE: MEMBRANE NEUROCHEM. SECT., DIV. NEUROSCIENCES, BECKMAN RES. INST. CITY HOPE, 1450 EAST DUARTE ROAD, DUARTE, CALIF. 91010.
 SOURCE: ANAL BIOCHEM, (1984) 140 (2), 510-519.
 CODEN: ANBCA2. ISSN: 0003-2697.
 FILE SEGMENT: BA; OLD

LANGUAGE: English

AB To streamline detection of calmodulin-binding proteins, blotting techniques for the electrophoretic transfer of proteins onto nitrocellulose **filters**, followed by overlay with ¹²⁵I-calmodulin, were adapted. Autoradiography of the ¹²⁵I-calmodulin-labeled blots allows the identification and quantitation of proteins that possess affinity for calmodulin. Five protocols for suppressing nonspecific binding and for enhancing specific interactions of ¹²⁵I-calmodulin with electrophoretically separated proteins were investigated. Tween 20 and bovine serum albumin alone, as well as combinations of bovine serum albumin and poly(ethylene oxide) or **Hb** and gelatin, were evaluated as quenching and enhancing agents. Tween 20 proved highly effective for quenching nonspecific binding and for enhancing specific ¹²⁵I-calmodulin binding of a 61,000-MW rat brain protein, which was only faintly observed on blots quenched with proteins alone. However, Tween 20 dissociated 50% of 68,000-MW proteins and 80% of 21,000-MW ¹²⁵I-labeled protein standards from the nitrocellulose **filter**. An alternative, the combination of bovine serum albumin followed by incubation with 15,000- to 20,000-MW poly(ethylene oxide), proved satisfactory for the recovery of 61,000-MW calmodulin-binding activity and for the detection of calmodulin-binding peptides (50,000 to 14,000 MW) produced by limited proteolysis of rat brain 51,000-MW calmodulin-binding protein. These blotting procedures for detection of calmodulin-binding proteins are compatible with a variety of 1- and 2-dimensional electrophoresis systems, including a 2-dimensional electrophoresis system utilizing urea and sodium dodecyl sulfate in the 1st dimension and nonurea sodium dodecyl sulfate electrophoresis in the 2nd, a system which proved useful for resolving calmodulin-binding proteins displaying anomalous electrophoretic migration in the presence of urea.

L22 ANSWER 12 OF 12 TOXCENTER COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1982:91005 TOXCENTER

COPYRIGHT: Copyright 2002 ACS

DOCUMENT NUMBER: CA09609062768X

TITLE: Renal toxicity of **hemoglobin** derivatives
as blood substitute

AUTHOR(S): Iwashita, Yuji; Ajisaka, Katsumi

CORPORATE SOURCE: Cent. Res. Lab., Ajinomoto Co., Inc., Kawasaki,
Japan.SOURCE: Organ-Directed Toxic.: Chem. Indices Mech., Proc.
Symp., (1981) pp. 97-101.
CODEN: 46XDAG.

COUNTRY: JAPAN

DOCUMENT TYPE: Conference

FILE SEGMENT: CAPLUS

OTHER SOURCE: CAPLUS 1982:62768

LANGUAGE: English

ENTRY DATE: Entered STN: 20011116

Last Updated on STN: 20011116

AB The relation between the clearance rate of infused **Hb** derivs. in the circulation of rats and their physicochem. properties was studied. When the mol. wt. of the **Hb** derivs. was .apprx.20,000, half of the infused deriv. disappeared in .apprx.30 min. When the mol. wt. was .apprx.40,000, the half-disappearance time was .apprx.50 min. In these cases, gross hemoglobinuria

appeared. Infusion of a series of polyethylene glycol-substituted Hbs revealed a close correlation between the retention vol. on gel chromatog. and the half-disappearance time. Apparently, the glomerular filtration of the Hb derivs. is analogous to the permeation through polysaccharide gel.

FILE 'REGISTRY' ENTERED AT 11:01:53 ON 17 OCT 2002

L23 4 S (ETHANOL OR METHANOL OR ACETONITRILE OR DIMETHYLSULFOXI
E DIMETHYLSULFOXIDE/CN 5
E DIMETHYLSULPHOXIDE/CN 5
E DIMETHYL SULFOXIDE/CN 5
L24 1 S E3
L25 5 S L23 OR L24

- claim 3

FILE 'HCAPLUS' ENTERED AT 11:02:54 ON 17 OCT 2002

L1 1 SEA FILE=REGISTRY ABB=ON PLU=ON "POLYETHYLENE GLYCOL"/C
N
L6 65224 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 OR APEG OR ACTIVAT?(W
) (PEG OR (POLYETHYLENE OR POLY ETHYLENE) (W) GLYCOL)
L10 42680 SEA FILE=HCAPLUS ABB=ON PLU=ON POLYOXYETHYLENE OR
CARBOXYMETHOXPOLYOXYETHYLENE OR METHOXPOLYOXYETHYLENE
OR POLY (W) (OXY ETHYLENE OR OXYETHYLENE) OR POLYOXY
ETHYLENE
L11 8 SEA FILE=HCAPLUS ABB=ON PLU=ON L10(10A) (ALPHA (W) (CARBOX
YMETHYL OR CARBOXY (W) (ME OR METHYL)))
L16 5 SEA FILE=HCAPLUS ABB=ON PLU=ON POE (S) (CARBOXY (W) (METHYL
? OR ME) OR CARBOXYMETHYL?)
L18 1 SEA FILE=REGISTRY ABB=ON PLU=ON "NYLON 66"/CN
L19 1 SEA FILE=REGISTRY ABB=ON PLU=ON POSIDYNE/CN
L23 4 SEA FILE=REGISTRY ABB=ON PLU=ON (ETHANOL OR METHANOL
OR ACETONITRILE OR DIMETHYLSULFOXIDE OR TETRAHYDROFURAN) /
CN
L24 1 SEA FILE=REGISTRY ABB=ON PLU=ON "DIMETHYL SULFOXIDE"/CN
L25 5 SEA FILE=REGISTRY ABB=ON PLU=ON L23 OR L24
L26 5157 SEA FILE=HCAPLUS ABB=ON PLU=ON (L6 OR L11 OR L16) AND
(L25 OR ETHANOL OR (ETHYL OR METHYL OR ME OR ET) (W) (ALCOH
OL OR ALC) OR METHANOL OR ACETONITRILE OR ACETO NITRILE
OR TETRAHYDROFURAN OR TETRA (W) (HYDROFURAN OR HYDRO
FURAN) OR TETRAHYDRO FURAN)
L27 826 SEA FILE=HCAPLUS ABB=ON PLU=ON (L6 OR L11 OR L16) AND
(DMSO OR DIMETHYLSULFOXIDE OR DI (W) (METHYLSULFOXIDE OR
(ME OR METHYL) (W) (SULFOXIDE OR SULPHOXIDE) OR METHYLSULPH
OXIDE) OR DIMETHYL (W) (SULFOXIDE OR SULPHOXIDE))
L28 38 SEA FILE=HCAPLUS ABB=ON PLU=ON (L26 OR L27) AND (HB OR
HEMOGLOBIN OR HAEMOGLOBIN)
L29 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L28 AND (L18 OR L19 OR
NYLON 66 OR POSIDYNE OR FILTER? OR FILTR?)
L30 0 L29 NOT L20

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, PHIC,
PHIN, TOXCENTER' ENTERED AT 11:08:31 ON 17 OCT 2002)

L31 1 S L29
L32 0 S L31 NOT L21

(FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO,
PHIC, PHIN, TOXCENTER' ENTERED AT 11:21:22 ON 17 OCT 2002)

L33 79 S "TALARICO T"?/AU
 L34 143 S "STACEY C"?/AU
 L35 11 S L33 AND L34
 L36 15 S (L33 OR L34) AND L17
 L37 18 S L35 OR L36
 L38 8 DUP REM L37 (10 DUPLICATES REMOVED)

L38 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:428940 HCAPLUS

DOCUMENT NUMBER: 137:2748

TITLE: Methods for the synthesis of a modified
 hemoglobin solution

INVENTOR(S): Privalle, Christopher Thomas; Stacey, Cyrus
 John; Talarico, Todd Lewis

PATENT ASSIGNEE(S): Apex Bioscience, Inc., USA

SOURCE: PCT Int. Appl., 45 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|------------|
| WO 2002044214 | A1 | 20020606 | WO 2001-US43877 | 20011114 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2002099175 | A1 | 20020725 | US 2001-930905 | 20010816 |
| AU 2002017823 | A5 | 20020611 | AU 2002-17823 | 20011114 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 2000-253758P | P 20001129 |
| | | | US 2001-930905 | A 20010816 |
| | | | WO 2001-US43877 | W 20011114 |

AB The invention concerns a filtration step during the Hb purifn. process that substantially decreases viral communication of a Hb soln. The filtration means can be used to sep. Hb and several endogenous antioxidant enzymes from red blood cell stroma and potential adventitious agents. The purified Hb/antioxidant compn. is then subjected to a chem. modification process. The resulting modified Hb /antioxidant compn. is then fractionated to remove unmodified Hb species and residual reactants, formulated in electrolytes and rendered sterile. The resulting modified Hb product is substantially free of viral contamination and contains at least one endogenous antioxidant enzyme that retains antioxidant activity.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
ACCESSION NUMBER: 2000:531386 HCAPLUS
DOCUMENT NUMBER: 133:246677
TITLE: Pyridoxalated **hemoglobin**
polyoxyethylene: a nitric oxide scavenger with
antioxidant activity for the treatment of nitric
oxide-induced shock
AUTHOR(S): Privalle, C.; Talarico, T.; Keng, T.;
DeAngelo, J.
CORPORATE SOURCE: Apex Bioscience, Inc., Research Triangle Park,
NC, USA
SOURCE: Free Radical Biology & Medicine (2000), 28(10),
1507-1517
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 97 refs. **Hbs** modified for therapeutic use
as either **Hb**-based oxygen carriers or scavengers of nitric
oxide are currently being evaluated in clin. trials. One such
product, pyridoxalated **Hb** polyoxyethylene conjugate (PHP),
is a human-derived and chem. modified **Hb** that has yielded
promising results in Phase II clin. trials, and is entering a
pivotal Phase III clin. trial for the treatment of shock assocd.
with systemic inflammatory response syndrome (SIRS). Shock assocd.
with SIRS is a NO-induced shock. PHP, a new mechanism-based
therapy, has been demonstrated in clin. trials to have the expected
hemodynamic activity of raising blood pressure and reducing
catecholamine use, consistent with its mechanism of action as a NO
scavenger. PHP is conjugated with polyoxyethylene, which results in
a surface-decorated mol. with enhanced circulation time and
stability as well as in attachment of sol. red blood cell enzymes,
including catalase and superoxide dismutase. PHP thus contains an
antioxidant profile similar to the intact red blood cell and is
therefore resistant to both initial oxidative modification by
oxidants such as hydrogen peroxide and subsequent ferrylHb
formation. These studies suggest both that the redox activity of
modified **Hbs** can be attenuated and that modified
Hbs contg. endogenous antioxidants, such as PHP, may have
reduced pro-oxidant potential. These antioxidant properties, in
addn. to the NO-scavenging properties, may allow the use of PHP in
other indications in which excess NO, superoxide, or hydrogen
peroxide is involved, including ischemia-reperfusion injury and
hemorrhagic shock.
REFERENCE COUNT: 97 THERE ARE 97 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L38 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2002 ACS DUPLICATE 2
ACCESSION NUMBER: 2000:405435 HCAPLUS
DOCUMENT NUMBER: 133:276101
TITLE: Comparison of various **hemoglobin**
polyoxyethylene conjugate solutions as
resuscitative fluids after hemorrhagic shock
AUTHOR(S): Glasgow, Sean C.; Shah, Ashish S.; Noone, Robert
B., Jr.; Gottfried, Marcia R.; Eachempati,
Soumitra R.; Talarico, Todd L.;
Vaslef, Steven N.

CORPORATE SOURCE: Department of Surgery, Wilford Hall Medical Center, Lackland AFB, TX, USA

SOURCE: Journal of Trauma: Injury, Infection, and Critical Care (2000), 48(5), 884-893
CODEN: JOTRFA; ISSN: 1079-6061

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Previous research suggested that splanchnic hypoperfusion occurs after resuscitation with certain acellular **Hb** solns. We examd. the influence of maltose content and oxygen affinity on resuscitation with various **Hb** polyoxyethylene conjugate solns. after hemorrhage. Methods: Fifteen swine underwent hemorrhage and equal vol. resuscitation with pyridoxalated **Hb** polyoxyethylene conjugate contg. 0% or 8% maltose, or low P50 conjugate, which also contained 8% maltose. Five control animals were monitored but not bled. Regional blood flow was detd. by using radioactive microspheres, gastric mucosal perfusion was estd. with tonometry, and gut histopathol. was evaluated. Results: All **Hb** solns. produced vasoconstriction, manifested by elevated mean systemic and pulmonary artery pressures without a significant decrease in cardiac index compared with the sham group. Resuscitation with maltose-contg. solns. elevated arterial and regional PCO2 and depressed arterial pH and gastric pHi ($p < 0.05$ for all). Splanchnic and renal blood flows were reduced in the low P50 + 8% maltose group ($p < 0.05$ vs. sham and baseline for renal blood flow), possibly indicating greater regional vasoconstriction in this group. Ileal mucosal damage was more severe in the maltose-contg. groups and correlated with decreased pHi. Conclusion: Vasoconstriction occurred in all groups but was more severe in the low P50 + 8% maltose group. Maltose-contg. solns. caused respiratory acidosis, decreased pHi, and histol. evidence of mucosal injury. Pyridoxalated **Hb** polyoxyethylene conjugate without maltose was a superior resuscitation soln. in this swine model.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:597438 HCAPLUS

DOCUMENT NUMBER: 136:289016

TITLE: Pyridoxalated **hemoglobin** polyoxyethylene conjugate (PHP): a nitric oxide scavenger containing SOD and catalase which reduces hemoprotein-mediated redox reactivity following oxidant challenge

AUTHOR(S): Privalle, Christopher; Keng, Teresa; DeAngelo, Joseph; Talarico, Todd

CORPORATE SOURCE: Apex Bioscience, Inc., Research Triangle Park, NC, 27709-2847, USA

SOURCE: Portland Press Proceedings (2000), 16(Biology of Nitric Oxide, Part 7), 146
CODEN: POPPEF; ISSN: 0966-4068

PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The relative susceptibility of pyridoxalated **Hb**

polyoxyethylene to hydrogen peroxide-mediated oxidns. was studied and compared to other Hb (Hb) derivs., including human Hb (HbA), and .alpha..alpha. XL. Exogenous catalase, added to a level typically found in PHP, prevented oxidative modification of HbA, which suggested that the resistance to hydrogen peroxide was due to the inherent catalase activity assocd. with PHP. Polyoxyethylene-HbA, a PHP deriv. lacking catalase activities, was susceptible to hydrogen peroxide oxidn. Spectral changes demonstrated differences among the various Hb derivs., with a rank order: .alpha..alpha.XL>HbA, POE-HbA>>PHP. PHP was resistant to hydrogen peroxide-mediated iron release, with only 2% of the total iron released by a level of hydrogen peroxide which released 50% of the iron in unmodified HbA. These results showed that PHP can reduce the prooxidant potential of Hb and suggested that specific modifications may reduce the potential toxicity of Hb-based therapeutics. PHP may also provide addnl. clin. benefits in specific applications, such as ischemia reperfusion injury treatment, a component of organ preservation media, and other Hb-based oxygen carrier/nitric oxide scavenger-dependent applications.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L38 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
ACCESSION NUMBER: 1999:793451 HCAPLUS
DOCUMENT NUMBER: 132:162551
TITLE: Chemical characterization of pyridoxalated
hemoglobin polyoxyethylene conjugate
AUTHOR(S): Talarico, T. L.; Guise, K. J.;
Stacey, C. J.
CORPORATE SOURCE: Apex Bioscience Inc., Research Triangle Park,
NC, USA
SOURCE: Biochimica et Biophysica Acta (2000), 1476(1),
53-65
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Pyridoxalated Hb polyoxyethylene conjugate (PHP) was developed in the 1980s as an oxygen carrier and is now under development for treatment of nitric oxide-dependent, vol. refractory shock. PHP is made by derivatizing human stroma-free Hb with pyridoxal-5-phosphate and polyoxyethylene (POE). A unique aspect of using POE for modification is that unlike its mono-methoxy polyethylene glycol (PEG) relatives, POE is bifunctional. The result of derivatization of stroma-free Hb is a complex mixt. of modified Hb and other red cell proteins. The mol. wt. profile, based on size exclusion chromatog., is bimodal and has av. mol. wt. of approx. 105,000 and 187,000. The mixt. of Hb mols. has on av. 3.3 pyridoxal and 5.0 polyoxyethylene units per tetramer. A portion of the tetramers are linked by POE crosslinks. The Hb tetramers retain their ability to dissoc. into dimer pairs and only a small percentage of the dimer pairs are not modified with POE. The SDS-PAGE profile exhibits the ladder-like appearance commonly assocd. with polyethylene glycol-modified proteins. The isoelec. focusing profile is broad, demonstrating a pI range of 5.0-6.5. The hydrodynamic size of PHP

was detd. to be approx. 7.2 nm by dynamic light scattering. Sol. red blood cell proteins, such as catalase, superoxide dismutase, and carbonic anhydrase, are present in PHP and are also modified by POE.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L38 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:628530 HCAPLUS
DOCUMENT NUMBER: 130:325
TITLE: Autoxidation of pyridoxalated **hemoglobin**
polyoxyethylene conjugate
AUTHOR(S): **Talarico, Todd**; Swank, Adam; Privalle,
Chris
CORPORATE SOURCE: Apex Bioscience, Inc., Research Triangle Park,
NC, USA
SOURCE: Biochemical and Biophysical Research
Communications (1998), 250(2), 354-358
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Hb**-based therapeutics are currently in clin. trials in the United States and abroad as blood replacement solns., nitric oxide scavengers, and radiation sensitizers. The potency of the therapeutics may be influenced by the oxidn. state of the iron in the heme moiety. The oxidn. state is dependent upon the phys. environment of the mol. and is influenced by parameters such as the chem. nature of the **Hb** therapeutic and its formulation. Pyridoxalated **Hb** polyoxyethylene conjugate (PHP) is one such compd. currently in clin. trials in the U.S. for treatment of nitric oxide-dependent, vol. refractory shock. The autoxidn. rates for PHP have been detd. over a range of temps. The oxidn. events were shown to be biphasic and were similar to those obsd. for purified human **Hb** (HbAo). The initial fast oxidn. events were modeled with first order rate consts. at 37 and detd. to be 0.022 h⁻¹ and 0.025 h⁻¹ for PHP and HbAo, resp. The autoxidn. of PHP was shown to be independent of concn. from approx. 5 to 100 mg/mL. (c) 1998 Academic Press.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L38 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:367271 HCAPLUS
DOCUMENT NUMBER: 129:159633
TITLE: Interactions of nitric oxide and peroxynitrite
with **hemoglobin** and PHP
AUTHOR(S): Privalle, C. T.; **Talarico, T. L.**;
Deangelo, J.; Keng, T.
CORPORATE SOURCE: Apex Bioscience, Inc., Research Triangle Park,
NC, 27709, USA
SOURCE: Portland Press Proceedings (1998), 15(Biology of
Nitric Oxide, Part 6), 302
CODEN: POPPEF; ISSN: 0966-4068
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Effect of NO on methHb and oxyHb levels was studied in HbA vs. pyridoxalated Hb polyoxyethylene (PHP). NO induced loss of oxyHb and a concomitant increase of methHb as a function of NO concn. The NO-induced loss of oxyHb and increase of methHb were similar for HbA and PHP. The possible use of PHP as NO scavenger is discussed.

L38 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2002 ACS DUPLICATE 4
ACCESSION NUMBER: 1997:393377 HCAPLUS
DOCUMENT NUMBER: 127:86186
TITLE: Detection of residual polyethylene glycol derivatives in pyridoxylated-hemoglobin-polyoxyethylene conjugate
AUTHOR(S): Miles, Paul J.; Langley, Kate V.; Stacey, Cyrus J.; Talarico, Todd L.
CORPORATE SOURCE: Apex Bioscience, Inc., Research Triangle Park, NC, 27709, USA
SOURCE: Artificial Cells, Blood Substitutes, and Immobilization Biotechnology (1997), 25(3), 315-326
CODEN: ABSBE4; ISSN: 1073-1199
PUBLISHER: Dekker
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purified Hb solns. have been shown to cause renal toxicity in animals. Safe use of Hb based therapeutics in humans requires modification of the Hb mol. to prevent this toxicity. Hb modification may be accomplished by crosslinking the dimers within the Hb tetramer or by derivatization of the .alpha. and/or .beta. subunits such that their size and/or charge prevents filtration by the glomeruli. Pyridoxylated Hb polyoxyethylene conjugate (PHP) consists of Hb mols. modified with .alpha.-carboxymethyl, .omega.-carboxymethoxy polyoxyethylene (POE). We have developed a high performance liq. chromatog.-based (HPLC) method which can quantitate residual POE at levels of 0.1 mg/mL or greater. The detection of POE at this level of sensitivity requires the use of an evaporative light scattering detector (ELSD). A differential refractometer may also be used for POE detection, however the limit of quantitation for this detector is approx. 10 fold greater than that obsd. for the evaporative light scattering detector, resulting in a redn. in sensitivity. The successful use of this method requires sample deproteinization using trichloroacetic acid. The reliability of the method has been demonstrated by spike recovery, precision, and reproducibility studies in PHP and buffer solns.

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